CHAPTER FOUR

Pharmaceutical chocolate

> "The pharmaceutical industry has spent tens, probably hundreds of millions of dollars in search of a chemical that would reverse … [or ward off vascular diseases]. And God gave us flavonol-rich cocoa which does that."
>
> (Norman Hollenberg, quoted in Paoletti et al., *Chocolate and Health*, 2012)

> "Enumerate the parts of a carriage and you have not defined a carriage."
>
> (excerpt from the *Tao Te Ching*, trans. McCarroll, 1982)

Like most other medicinal plants and foods, Cacao contains an array of pharmacologically active chemicals. In the natural pharmacopoeia, there's no sharp division between foods and drugs; these distinctions are flexible, and often based on the use to which a plant is put—food or medicine—rather than its chemistry alone. Medicinal plants such as chamomile (*Chamomilla recutita*) or white willow bark (*Salix alba*) contain fewer toxic compounds than the poisonous leaves and shoots of the common potato plant (*Solanum tuberosum*), or other culinary staples such as cassava or manioc (*Manihot esculenta*), the tropical tuber which is a staple food in parts of South America and Africa, or kidney beans (*Phaseolus vulgaris*), which require soaking and thorough cooking to make them edible. Plants such as carrots, garlic, fennel, and barley have both edible and medicinal uses. Foods can have profound effects on health, positive or negative—witness research into the health-promoting effects of so-called "phytoestrogens" in soya beans, capillary-strengthening antioxidants in bilberries, and compounds in tomatoes and pumpkin seeds which retard the onset of prostate enlargement in men (amongst other things).[500]

Many interactions between plant and *Homo sapiens* chemistry are fundamentally important to human health or disease, such as the requirement for vitamin C from fruits and vegetables to prevent scurvy, or, on the flip side, the inherited sensitivity to gluten in some cereal crops which causes the digestive disorder known as coeliac disease, to name but two. These effects are a result of our co-evolution with plants. Plants are our primary and original source of food and medicine, as well as building material, paper, various fabrics, and dyes (to say nothing of oxygen); they have influenced us chemically, metabolically, environmentally, and behaviourally from the start. We are plant-interdependent organisms.

The point of all this is that the original Hippocratic maxim "let food be your medicine" is poorly understood in this pharmacophilic era. Population studies show that

> Cardio-vascular disease [CVD], including stroke, is the leading cause of death and disability in developed countries. […] Diet is a major factor contributing to the onset and development of CVD […] Defining specific modifications of dietary habits in a population can have a major impact on CVD, especially during the long period in which the disease is silent. (Galleano, Oteiza, & Fraga, 2010)

This is to say nothing of the presumed longer-term influence of diet and lifestyle on diabetes, cancer, senile dementia, or a host of other interlinked "Western" diseases of affluence. The biomedical model's preventive strategy for dealing with these issues is to provide generic dietary and lifestyle advice (eat fruit and vegetables, don't smoke), or to use powerful, potentially harmful drugs to reduce single risk factors for specific health problems, leaving commercial enterprises to market various "alternative" novelty pills as unproven magic bullets for disease prevention in the form of the multi-million dollar vitamin and supplements industry.

Our pharmacophilic mentality originates in large part from the post-Paracelsan[vi] conceit that any medicinal plant is equivalent to its "main active principle", a notion which has been disproved time and again by clinical and pharmaceutical research into the effects of medicinal plants versus their chemical offspring. It now seems laughably simplistic to say of a plant, "This is the bit that makes it work—the rest of it's garbage," a bit like saying that apples are only vitamin C with packaging. It is naïve to dismiss some compounds as irrelevant on the basis that they are "inert" (they have no apparent pharmacological activity on their own) or "trace" (there's too little to have any biological relevance). The intricacies of metabolism may mean that what at first appears to be so much chemical filler actually turns out to influence the effect of the whole plant once ingested, by interacting with other compounds in the drug or in the living body ("*in vivo*"), sometimes in surprising ways. The most pharmaceutically active compounds produced by plants are referred to as "secondary metabolites", which were

> once regarded as simple waste products of a plant's metabolism. However this argument is weakened by the existence of specialist enzymes, strict genetic controls, and the high metabolic requirements of these compounds … Today most scientists accept that many of these compounds serve primarily to repel grazing animals or destructive pathogens. (Pengelly, 2004)

Even this is a reductionist view. These compounds are so variable in type and quantity, from species to species and even intra-species, that is, from daisy to daisy, or nettle to nettle—depending

[vi] "After Paracelsus", aka Philippus Aureolus Theophrastus Bombastus von Hohenheim (1493–1591), the surgeon, alchemist, astrologer, and lecturer who is credited with originating the pharmaceutical obsession with using powerful and specific chemicals or drugs in medicine, as a result of his advocacy for mineral remedies and alchemically 'purified' plant extracts. He was a notable empiric, despised tradition to the extent of publicly burning the collected medical works of Galen and Avicenna, and was one of the early pioneers of antisepsis in wound dressing, advocating cleanliness first and foremost in wound healing.

on the age and location of the plant, its growing conditions, and many other factors—that they represent a kind of pharmacological "fingerprint".

When medieval alchemists distilled volatile aromatic compounds from medicinal plants they characterised these so-called Essential Oils as the physical vehicle of the Soul or Spirit of the herb, because of their distinctive and penetrating smell, so intensely redolent of the source plant. In a similar way, secondary metabolites in general may be seen as a plant's "chemical character", its unique molecular personality profile. Their physical effects when ingested by different organisms are as much a product of their co-evolution with other species as the behavioural adaptations of humans and other animals to their environment, reflecting levels of interactive complexity in survival strategies which go far beyond chemical warfare. For example, plants such as the opium poppy or the Cacao tree which humans find useful may be cultivated, and this cultivation will often maximise production of those much-desired "secondary metabolites"—ensuring the plant species' survival, dissemination, and adaptation through involvement with the aggressively expansionist mammal, *Homo sapiens*. To what extent this may be thought coincidental when one can observe incredibly complex inter-species evolutionary survival tactics throughout nature is debatable.

So examining the chemistry of foods or medicines (and Cacao has a branch in both camps) can help us understand them further, as an aid to defining their nutritional or medicinal uses, as long as this pharmacognostic approach is used alongside traditional knowledge, and filtered by common sense. It also demonstrates very clearly the remarkable and irreproducible, irreducible complexity of natural pharmacy, and the need to evolve from our current medical-pharmaceutical model towards a more integrative and holistic approach.

Scientific objectivity, clinical research, and chocolate in action

> "The placebo effect … one of the most powerful forces in our lives—the biological consequences of social, human, and meaningful interaction—[has] been tossed into the ash [*sic*] can." (Moerman, 2002)

Most research on medicinal plants and foods is limited to one condition, or focused on one outcome, such as blood pressure, pain, or whatever factor the researchers are interested in. The evidence-based medical research model for testing drugs begins with lab research (*in vitro*, meaning "in glass", i.e., in the laboratory), progresses to live test animals such as rats (*in vivo*—meaning "in life"), and—finally, if the substance is shown to be useful—in human clinical trials. The "gold standard" clinical trial model is the randomised double-blind placebo-controlled clinical trial. In these trials the substance or treatment in question is given to one group, another group is given a fake "placebo" treatment, and there is often a third group, the "control" group, which is given no treatment at all. The participants are matched in terms of participation criteria such as age, weight, sex, etc., then randomly split into groups. Most important, steps are taken so that neither the researchers nor the participants know who is taking the real treatment and who is taking the placebo until after the trial is over, to prevent the researchers accidentally or deliberately influencing the participants. This type of design is used to verify "real" effects of treatments, as most interventions will produce strong *placebo* or *nocebo* effects, that is, the belief of the participants—or the researchers—about who is receiving the "active" treatment will create some medicinal benefits (placebo) or unpleasant side effects (nocebo), so it's important to distinguish these *psychosomatic* (mind-body) effects from the "genuine", "objective" effects of a treatment.

Sometimes a double-blind trial isn't possible, for example if you were testing, for reasons best known to yourself, the effects of bungee jumping on hair growth—it can be hard to fake the real thing. In such cases, to give more reliable results, no placebo is used; instead, larger numbers of people may be recruited into the trial, all partaking of the "real" treatment, and compared to an equal-sized group of participants receiving no treatment at all. Because these "open" trials don't reduce the impact of the mind-over-matter placebo effect as much as double-blind trials, they often give stronger positive results for the treatment under scrutiny. But what tends to be forgotten is that this doesn't reduce the *practical* importance of positive results in less well controlled studies. Pragmatically, it doesn't matter if the effectiveness of a drug is pharmacological or psychological, so long as the results are *consistent* and *replicable*. Placebo is a fancy way of saying "genuine medical effects of non-pharmacological origin". What placebo does *not* mean is "ineffective". In his penetrating book on the placebo effect, Professor Daniel Moerman argues that the phrase "placebo effect" should be changed to "meaning effect", as the seemingly magical powers of placebo depend largely on the depth and nature of the cultural, symbolic, and emotional *meaning* which the treatment has for patients and therapists.[501]

The inner workings of the meaning (placebo) effect can be mind-blowing. In the case of angina, a condition where blood flow to the heart is restricted and causes chest pain, physicians who are enthusiastic about their treatment cure 70%—90% of their patients, whereas those who doubt its efficacy cure only 30%—40% of their patients, using identical treatments. Old drugs and surgical procedures become measurably less effective the moment new treatments come along. Advertising and branding increase the medicinal effectiveness of all drugs. The colour and shape of a pill alter its effects on people, and the nature and magnitude of effects vary in different locations and cultures. Placebo treatments produce measurable physical changes just like a "real" drug, such as opiate release (painkilling), and can cause other physical changes identical to a "real" drug, including side effects, and this can happen *even when patients are unaware that these effects would normally occur*. Simply including patients in a study—just putting them under observation—improves health outcomes. Patients with a view of plants or greenery from their hospital room have better recovery rates than patients with a plant-free hospital experience.[502] These are all examples of the meaning effect at work.

The "number needed to treat" in a placebo-controlled clinical trial of a pharmacologically effective drug varies, but the phrase refers to the number of patients who benefited in the group who received the "real drug" as compared to the "placebo"—and this number is often surprisingly small. It's thought that, like hypnosis, being susceptible to the placebo effect must depend on individual psychology or beliefs, perhaps to some sort of suggestibility or credulousness—but it turns out, that isn't the case, and all of us are equally susceptible to its benefits. What does matter, greatly, is the belief of the doctor or treatment administrator: as in the angina trial above, their degree of confidence will be mirrored in their results. The often remarked-upon "arrogance" of top surgeons, doctors, and charismatic therapists, it turns out, may be an essential ingredient of their success, and not simply because they are tirelessly (or tiresomely) self-promoting.[503] Placebo has become a dirty word; we of the modern, post-industrial world are so hung up on finding out how a medicine or procedure is "really working", that we sometimes minimise the most important matter, which is how well a given medicine or treatment works *in real life*.

Additionally, the biomedical model of drug testing—from lab, to animal, to human trials—sometimes misses important things. Say a plant is traditionally used in the treatment of cancer, and researchers apply an extract of that plant to some cancer cells in the laboratory, and it doesn't have any effect on them. The plant is then discarded, and not investigated any further. But what if that plant only produces effects on cancer in living human bodies, and doesn't act on cancer cells directly? It may work through secondary mechanisms, such as enhancing the immune response to specific cancer cells, or even more indirectly, by altering the composition of microbes in the gut which may in turn influence the immune response or produce cancer-retarding compounds. If cancer is an armed robber, the lab screening will find all the plants who are like trainee policemen. It won't detect the plants which are like surveillance camera operators, or like people who call the police to tell them a robbery is in progress, or like effective prosecution lawyers—only the ones which may eventually be directly involved in the process of stopping cancer, if they pass the tests!

So what, then? How are plants or substances that were traditionally used for a condition, but may not act directly, tested? In the current system, they often aren't. The issue of the questionable relevance of some research is public knowledge. Frankie Boyle said it well: "Shall we have a go at curing cancer? No. I'm going to see how many fruit pastilles it takes to choke a kestrel."

So reality isn't found in the artificially restricted conditions of a laboratory experiment or a clinical trial. "Evidence-based medicine" tests should be used as a method to help determine which of two treatments is *more effective*, and what *proportion* of a treatment's measurable benefit is down to the drug or procedure, in other words how much of its effectiveness depends on the meaning ("placebo") effect. Whether it's effective or not can simply be determined by a statistical analysis of a given treatment's real-life performance: whether the majority of patients so treated feel better and live longer, or not. Put over-simply, randomised double-blind placebo-controlled clinical trials reveal how much of a given medicine's effect is mind over matter—aka the *vis medicatrix naturae*, nature's inherent healing power, or the sum total of reparative psychobiological processes—which we call "placebo". The medical reality is to be found in the real world, under real conditions, in which the perceived character and symbolic qualities of all medical interventions of any kind are integral to their effectiveness.

We also know that drug plants are complex entities, producing complex effects. The chemicals in a substance such as Cacao can interact in the body in several ways. Some compounds of plant origin may not be found in the whole plant at all, but are created in the human body from the original plant chemicals; these original compounds may be utterly transformed by metabolic processes in the digestive system or liver, or by some of the billions of microscopic organisms living in the gut, for example. Very simply put, the different pharmacologically active compounds in a single medicinal plant can inhibit, enhance, or do nothing at all to affect how they work together. Enhancement can occur in two ways: it can be *additive*, meaning that chemicals simply add their effect to one another (1+1 = 2), or it can be *synergistic*, meaning that the total effect of the two chemicals is far greater than would have been expected (1+1 = 11). Likewise, they can inhibit each other by *antagonism*—they simply cancel each other out, one activates and the other deactivates (1+ –1 = 0)—or by *competitive inhibition*, where both chemicals are trying to do the same job in the same place at the same time and they get in each other's way, like two footballers on one team trying to kick the ball simultaneously and tripping each other up (1–1 = 0). So the overall effect of a medicinal or pharmacologically active plant in the body is the result of how all its constituents work together. In other words, every plant has a sort of chemical personality, and where the "ingredients" all mesh well as regards a particular action on human physiology, they can produce noticeable effects. Because of this complexity, most medicinal plants alter bodily functions with brush strokes and mixed colours, rather than the relatively straight lines and primary colours of pharmaceuticals.

Cacao, too, contains many different compounds, which contribute to its nutritional profile, its flavour, and its medicinal effects. So to attain a better understanding of chocolate, we will look at the chemical composition of Cacao and its botanical accomplices.

Filleting the bean

Before enumerating Cacao's parts, we should keep in mind that looking at individual substances from any natural product is often quite misleading, because there are so many compounds in one plant (or animal, for that matter). Not all of the chemicals in Cacao will be absorbed from the human digestive tract, depending how the bean is ingested, and not all of those which are absorbed will remain chemically active for very long once the liver does its work; and some will enhance or inhibit the absorption or effectiveness of others. How, in what form, and when the Cacao is consumed will also influence matters, as (most importantly) will the state of the organism consuming it: for example, whether they have a full or empty stomach, what else they have recently eaten or drunk, their age, weight, sex, baseline mood, etc.

Clinical science gets round this problem by using statistics and controlled conditions to arrive at average outcomes and attain consistent, reproducible data for each component, disregarding "anomalous" results. Averages and controlled situations don't always reflect reality though, otherwise all Western adults would be married and live in a semi-detached house with 2.5 children and half a pet with a stable income of whatever the current national bell curve suggests. As described in the last chapter, traditional medical systems account for individual differences by observing and classifying different plants, people, illnesses, ages, times of year/day, etc. in terms of their different characteristics, in order to predict outcomes and guide treatments, but often do so in allegorical, empirical ways, such as describing particular organs of the body or foods or drugs as Hot and Dry or Cold and Wet, or making connections between illnesses and the time of year, the weather, or personal temperament. The drawback of such traditional medical systems is that inappropriate or ineffectual treatments are harder to spot, because they are based on subjective results which can depend on many different factors, and are concerned only with individual outcomes, not with statistical evidence. Nevertheless it should be recognised that from a real-world, individual perspective, reality is much more idiosyncratic than statistics suggest. With this caveat, the chemical compounds in Cacao seeds are to be analysed using the following categories:

- **Pharmacodynamics (pD)—**what they do in the body
- **Pharmacokinetics (pK)—**how well they're absorbed and distributed around the body, and what factors affect this, and
- **Interactions**, which may be synergistic, additive, or inhibitory.

For a detailed account, please see the monograph in Appendix A: this chapter will gloss and summarise the findings, so as to be more digestible. After that, it will be useful to look at other plants used alongside Cacao in traditional chocolate drinks, and how they are likely to affect each other's pharmaceutical activities and the overall quality of these preparations. Some of the conclusions are speculative and based on a combination of observation, known chemistry and pharmacology, anecdotal reports, and logical deductions, *in lieu* of comprehensive clinical data; but, as the saying might as well go, you can't make chocolate without shelling a few beans.

Cacao chemistry

Chocolate chemistry, like that of many natural products, is extremely complex. Cacao contains a large number of biologically active and bioavailable compounds ("bioavailability" refers to the capacity for a substance, whether nutrient, drug, or toxin, to be absorbed and reach its site of action or use in the body, the "target tissue"). When human volunteers' urine was analysed 24 hours after consuming chocolate,

> 27 metabolites related to cocoa-phytochemicals, including alkaloid derivatives, polyphenol metabolites (both host and microbial metabolites), and processing-derived products such as diketopiperazines were identified. (Paoletti et al., 2012)

Translating the pharma-jargon, this tells us that many of the various plant chemicals ("phytochemicals") in Cacao had made their way through the body, some of what remained was still being excreted in the urine twenty-four hours later, and many of the chemicals were created by microbes in the human gut, using the chemicals in the plant.[504] In other words, the eventual effects of Cacao, or of any medicinal plant, are not only dependent on the chemicals the original drug contains, but on the complex array of chemicals produced by our bodies, and the smaller microbial bodies inhabiting them.

The following chart is a visual representation of the different groups of chemical compounds found in toasted Cacao seeds.

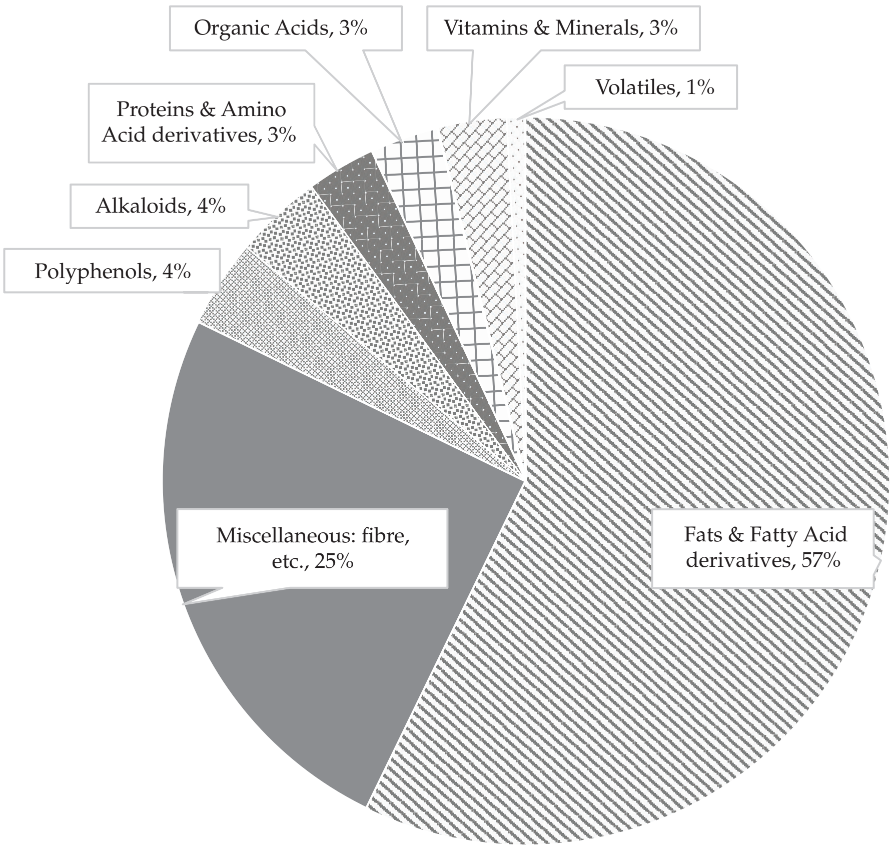

Figure 2. Approximate chemical composition of toasted *Theobroma Cacao* seeds, as % dry weight.

Over half of the seeds are composed of fats and related substances, with approximately 15%–25% carbohydrate (standardised to 18% in Figure 2)—these carbohydrates are "fibre" such as cellulose and pectin, and naturally occurring sugars. This "filler" may still affect the properties of the seed once ingested, by modifying the absorption of other constituents, or providing food for gut microbes. The more pharmacologically "active" material—the alkaloids, polyphenols, amino acid-based compounds, organic acids, vitamins, and minerals—comprise up to a third of the seeds' dry weight.

Bulking: fats and miscellaneous constituents

The combination of fatty acids in Cacao, collectively referred to as "cocoa butter", has the useful property of being liquid at body temperature but solid below 25° Celsius (77° Fahrenheit), enabling chocolatiers to produce chocolate that melts in your mouth (or your hand, or your pocket, or on a hot day). Fats are calorie-dense, and provide some rationale for Cacao's traditional reputation as a food-drug for weight gain and convalescence. Approximately 34%

of Cacao's fat content is made up of "bad" saturated fats, the kind linked to heart disease—except in this case, just over half that is *stearic acid*, a type of saturated fat which lowers "bad" LDL cholesterol. When applied to the skin of tortured mice, stearic acid sped up the healing of burns,[505] which corroborates the traditional usage of cocoa butter for healing damaged skin. The remainder comprises "heart-healthy" mono- and poly-unsaturates. It should be noted that the fatty acids in cocoa butter tended to increase blood coagulation and blunt insulin sensitivity in the lab, effects which are outweighed by the potency of Cacao's polyphenols. Nevertheless this is another good argument for consuming traditional Cacao beverages rather than eating chocolate bars, with their added fat content.

The fatty portion of the seeds also contains a small quantity (about 0.2%) of *phytosterols*, hormone-like compounds which help to prevent several types of cancers and reduce cholesterol absorption from the intestines. The quantity of these compounds in Cacao is not exceptionally high, but 20mg of the phytosterol *β-sitosterol* taken three times daily, equivalent to the amount found in 40–80g Cacao seeds (comparable to the daily dose found in high-potency Cacao beverages), has been found to reduce the symptoms of prostate enlargement in older men.[506] These compounds also improve immunity and reduce the immediate stress effects of hard exercise on the body and the immune system.[507] A tiny proportion of Cacao's fats are made up of compounds called *phospholipids*, which are surfactants (a kind of emulsifier, or "soap", which helps make water-soluble compounds more fat-soluble, and vice versa). These phospholipids, though small in quantity, increase the absorption and effectiveness of some of the polyphenols in Cacao[508]—another example of how the pharmacological actions of a drug plant are the sum of its parts.

Buffering: polyphenols

> "*One serving* of dark chocolate is thought to impart a greater antioxidant capacity than the average amount of antioxidants consumed daily in the United States." (Castell et al., from Watson et al., 2013, my italics)

Much has been made of Cacao's "antioxidant" properties, resident in the *polyphenols*, a group of compounds which collectively comprise about 4% of the toasted beans' weight. Antioxidant properties are measured by a scale called oxygen radical absorbance capacity (ORAC), and polyphenols are a large group made up of tannins (sour- and dry-tasting molecules which make the inside of your mouth pucker when you drink black tea without milk) and many smaller compounds. Chocolate contains the highest weight of polyphenols in any food,[509] and freshly prepared un-Dutched cocoa powder (the powdered and de-fatted bean) has a higher ORAC level by far than blueberries, red wine, and many other foods.[510] But the antioxidant effects of Cacao, which are often touted as its main benefit, should be viewed with caution—because many of the medicinal effects of the polyphenols in Cacao may turn out to be independent of their antioxidant properties *per se*.

"Antioxidant" is a bit of a sloppy generic term for a very wide range of natural and synthetic substances, all of which share that one common feature but may be quite different in terms of their effects in the living human organism. Antioxidants are substances that mop up *free* *radicals*. Despite the name, free radicals are not in fact tiny Che Guevaras; they are molecules with missing electrons. This means they lack one negatively charged particle, and are electrically unbalanced, so they steal electrons from other atoms to stabilise themselves. Free radicals are generated like dirty smoke by ordinary cellular activity, causing damage as they rip electrons away from other atoms and ultimately destabilise the cells those atoms are part of; they degrade cell structure "one brick at a time". Antioxidants are substances with spare electrons, so they donate an electron to a hungry free radical, and rebalance it.

A theory called *mitohormesis* proposes that free radicals (or "reactive oxygen species" [ROS], to give them their proper name) are actually necessary to promote long life. By acting as stressors produced by the engine of the cell (the *mitochondria*, after which the theory is named), free radicals/ROS induce the cell's energy production to become more efficient.[511] Just as oysters make pearls as a result of the irritation produced by grains of sand, so the mitochondria require just enough—and not too much—free radical activity to prolong the cell's life. So seeing free radicals only as "bad guys" to be zapped by antioxidants is too simplistic.

Cacao compounds exert antioxidant activity in several ways: they directly neutralise free radicals by donating an extra electron to them in the usual way; they inhibit enzymes which produce reactive oxygen species (a type of free radical); and they "chelate metal ions"—in other words, attaching themselves to little electrically charged metal atoms and smothering their charge, like little brown fire blankets. Some other compounds in Cacao, the xanthine alkaloids (theobromine, caffeine, and theophylline) play a role here too, as they are also metal ion chelators.[512] The theory goes that the antioxidants in Cacao neutralise free radicals and promote release of nitric oxide from the linings of blood vessels, causing them to dilate, and improving blood flow.[513] In fact these effects are all mediated by very specific sequences of interactions between particular polyphenols and enzymes in the body; you couldn't just chuck some "antioxidant-rich" blueberry/acai/whatever juice into a blood vessel and expect exactly the same effect. One example of this is the well-researched flavonoid (a type of polyphenol) called epicatechin, found at high levels in Cacao and green tea. Epicatechin protects heart cells from injury not by antioxidant means, but by binding to opiate (endorphin) receptors in the heart, which blocks some injury-causing chemical chain reactions that occur when cells are deprived of oxygen.[514]

We do know that Cacao, once eaten, significantly increases the antioxidant level and reduces lipid (fat) oxidation in the blood, which is generally good: this indicates that Cacao most likely counteracts tendencies to *atherosclerosis*, or "furring up" of arteries and blood vessels, and may therefore reduce the risk of developing heart disease. But, interestingly, excessively high levels of Cacao flavanols can become *pro-oxidant*, especially in the presence of metals which react with oxygen (any metal which tarnishes or rusts, e.g., iron or copper). This fact will become especially relevant when looking at possible links between Cacao and Parkinson's disease in Chapter 7. Moreover, some studies showed that Cacao appeared to have significant health benefits, even in the absence of any obvious antioxidant effects.[515] This also suggests that the undoubtedly high antioxidant capacity of Cacao may not be directly related to its health benefits; the fact that some of Cacao's most "health-promoting" compounds may turn out to be antioxidants doesn't necessarily suggest that Cacao can be substituted with other high-antioxidant foods or substances in the expectation of achieving the same results, just as forcing a vet to stand in for a professional lion tamer may not go well, even if they are both used to handling cats.

The greater proportion of Cacao's polyphenols (see Figure 3 below) is made up of *lignin*, a form of indigestible fibre which helps to feed good bacteria in the gut. Lignin is a common compound found in many types of plant material, which probably exerts few direct effects, although some anti-viral activity has been noted in the laboratory.[516] Of the remainder, the procyanidins and flavan-3-ols are the subject of intense research. *Criollo* Cacao (the "posh" variety, traditionally used by the Maya and Mexica) contains no *proanthocyanidins*, red-purple compounds which break down to yield smaller *procyanidins*, but it does contain high levels of *flavanols* (technically, flavan-3-ols) and the procyanidins themselves, so its antioxidant properties are the same, in effect, as the other varieties with higher levels of polyphenols and the sourer-tasting proanthocyanidins.[517] Cacao polyphenols as a whole, if consumed regularly, have been shown to prevent or delay the development of several types of cancer in animal experiments, including prostate cancer in rats, at levels of intake which may be achievable with traditional Cacao beverages.[518] The polyphenols also increased lab animals' lifespans, improved their memories, protected them from heart disease, lung damage, and peptic ulceration, and reduced clotting risks.

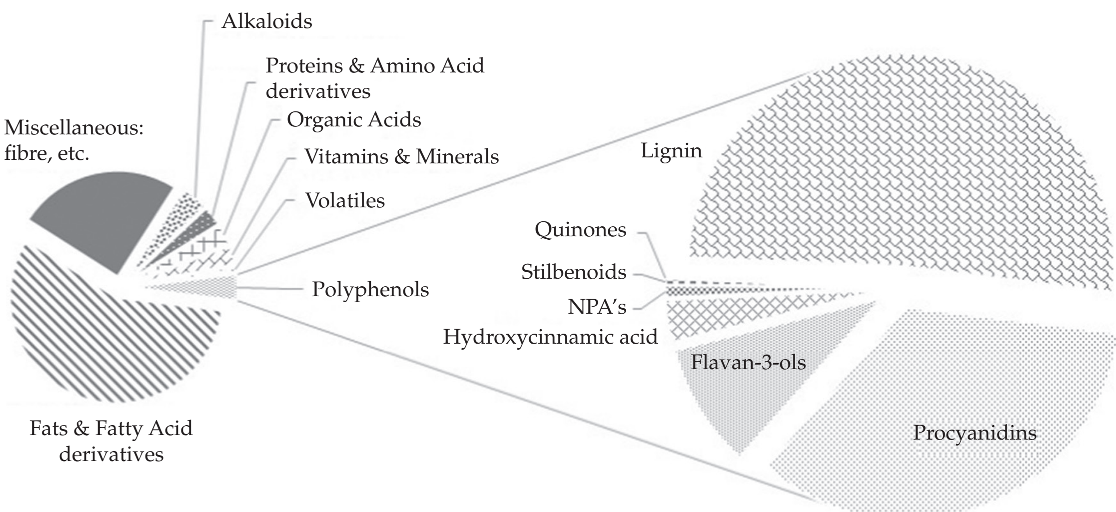

Figure 3. The polyphenols in *Theobroma Cacao* seeds.

In addition to being associated with a reduced risk of heart disease and stroke in humans, the flavanols may also improve cognition. In animal studies, they accumulate in parts of the brain associated with learning and memory, and in human studies, higher levels of dietary flavanol intake are linked to better brain function in aging and age-related diseases such as dementia and stroke.[519] Lab research into the procyanidins show potential anti-cancer activity, and complex, modulatory effects on the immune system and inflammation.[520] Lab and animal research suggests that the flavanols in Cacao also reduce inflammation, alter immune system protection of the lining of the airways and digestive tract, enhance levels of "happy" brain chemicals such as dopamine and phenethylamine by reducing the rate at which they are broken down, protect the heart, thin the blood like aspirin, and reduce the risk of developing gum disease.[521] These compounds have been shown to get into the system after ingesting Cacao, and blood levels peak two hours after consumption.[522]

Many of the smaller polyphenols such as the flavanols and procyanidins are manufactured from larger molecules (*flavonoids* and proanthocyanidins, respectively) by gut microbes, so the exact effects of whole chocolate in each person's case will be modified by the state of their digestive tract. The terrain of the gut, as is often the case, influences the effect of the medicine—and vice versa, as the polyphenols' effects on immunity and the gut lining will affect the microbes living there. However, milk almost halves the level of Cacao flavanols detectable in the bloodstream after consuming chocolate, because the proteins in milk bind to the polyphenols and reduce their absorption. Conversely, sugars and starches increased their absorption significantly[523]—although added sugars (glucose, fructose, sucrose, honey, or even fruit juices) are known to reduce the immune response for several hours after consumption (specifically, the ability of some "first-line" immune cells, white blood cells known as neutrophils, to ingest or "phagocytose" bacteria is suppressed for several hours following the consumption of these sugars, an effect which doesn't occur with whole fruit).[524] On the other hand, complex carbohydrates such as *masa harina* flour will break down and yield sugars in the gut, where they may assist the absorption of Cacao polyphenols, while also providing beneficial insoluble fibre to feed "friendly bacteria" in the large intestine—without flooding the system with free sugars, which may spike insulin, reduce immunity, and encourage the overgrowth of less beneficial gut microorganisms. Yet more reasons to take chocolate without milk and with only complex carbohydrates such as maize, or with very little added sugar, in the traditional Mesoamerican style.

Some of Cacao's trace polyphenols, such as *caffeic acid*, also help to protect liver and blood vessel cells from injury,[525] and the *phenolic acids*—formed during fermentation of the bean—may provide some protection for the pancreas (the organ which controls blood sugar), the stomach lining, the heart, and the kidneys, and contribute to Cacao's pain-reducing and anti-inflammatory properties[526] if the lab results and animal experiments are anything to go by. The *hydroxycinnamic acids* in Cacao have similar effects in the test tube, reducing blood sugar, protecting immune cells, and brain cells, and liver cells from injury.[527] However, the principal hydroxycinnamic acid in Cacao, *chlorogenic acid*, may also inhibit vitamin B1 (thiamine) absorption from foods when Cacao is consumed with them, although this is disputed.[528] Trace compounds known as *NPAs* (N-phenylpropanoyl-l-amino acids, to give them their full title) also protect brain cells from injury, reduce blood clotting and inflammation, and dilate the airways.[529] Pharmacologically active levels of NPAs have been found in the bloodstream of humans two hours after eating chocolate.[530]

The *stilbenoids* include the well-researched *resveratrol*, red wine's much trumpeted "miracle" health-promoting compound. Resveratrol raises the level of stimulating brain chemicals such as dopamine and phenethylamine by preventing their breakdown (of which more later), but its predicted anti-aging, brain- and heart-protecting, and anti-cancer properties from results in the lab don't seem to translate well to real-life trials using the isolated compound.[531] That said, resveratrol administered to human volunteers over a one-year period in combination with other polyphenols did reduce blood markers of inflammation.[532] So it's possible that the stilbenoids in Cacao have measurable effects in conjunction with the other phenolics, even though the amount is small. While there are very tiny, sub-active amounts of *quinones* in Cacao, these substances have the rare property of being able to rejuvenate old cells by stimulating the mitochondria—the cell's energy-producing battery—to repair themselves, and have been shown to reduce harmful effect of stress in humans.[533] It's unknown how all these compounds interact, but it's striking that many have similar effects, and the possibility of these effects "stacking up" and adding up to something considerable is very real, particularly if the results from human trials with whole chocolate, detailed later in this chapter, are anything to go by.

Accelerating: alkaloids

One of the most notable (and popular) groups of compounds in Cacao are in the class known as alkaloids, so named because these molecules contain nitrogen, giving them an alkaline pH. They're popular because they're principally responsible for Cacao's stimulating, mood-lifting effect, though there are other components at work here, too. Alkaloids are found in (and extracted from) many other world-famous recreational plant drugs such as coca leaf, coffee, khat, kratom, opium, tea, and tobacco, although alkaloids in general are a very diverse group of chemicals: not all plants that contain alkaloids affect the brain, and not all chemicals that affect the brain are alkaloids. The alkaloids comprise around 4% of the weight of toasted Cacao, neck-and-neck with polyphenols (see Figure 4).

The primary alkaloids in Cacao are the three so-called *xanthine alkaloids*, theobromine, caffeine, and theophylline, plus a sprinkling of other trace compounds—salsolinol, the tetrahydro-beta-carbolines (THβC's), the pyrazines, and trigonelline. Of these, *caffeine* is the most stimulating, acting by blocking a sedative brain messenger (neurotransmitter) called adenosine so that "signal amplification" occurs in various parts of the brain. Caffeine is partly responsible for many of Cacao's mind-altering effects, as lower doses (up to 250mg), such as may be found in coffee, tea, or a real chocolate drink, generally increase feelings of sociability, confidence, and good mood, raise pain thresholds, and provide a weak generalised stimulation to the pleasure and habit-forming regions of the brain. Caffeine enhances the action of the brain chemical *dopamine* in these areas, which generates both pleasure and motivation. Despite this, only lower doses of

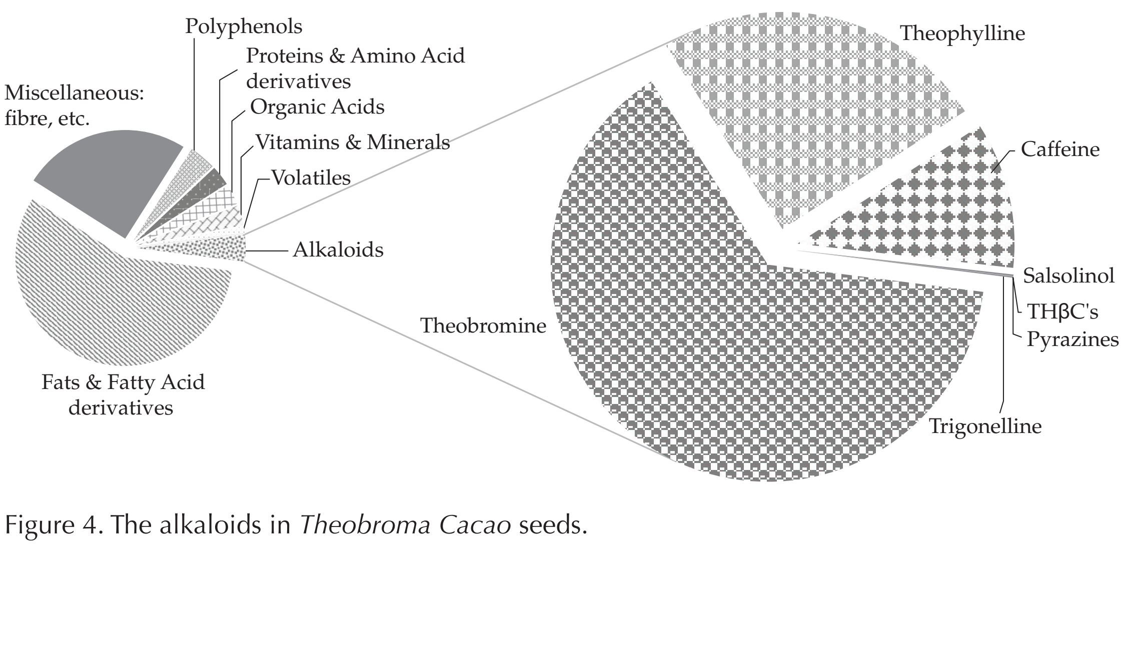

Figure 4. The alkaloids in *Theobroma Cacao* seeds.

caffeine (such as those found in Cacao) resemble the effects of more powerful dopamine-releasing drugs such as cocaine or amphetamine in the principal brain region involved, the *nucleus accumbens*. Higher doses of caffeine—as anyone who has overdone the coffee can testify—don't have such a pleasurable effect, and end up making the user feel uncomfortably overstimulated, anxious, and jittery. In science lingo, higher doses of caffeine become aversive.

Cacao contains around 0.2% caffeine,[534] but a 40g dose of Cacao seed which may be consumed in a traditional Cacao-based beverage contains 84mg of caffeine, greater than the amount in a cup of tea. *Criollo* Cacao beans, the variety of Cacao with the longest pedigree, and still the preferred variety for chocolate connoisseurs and makers of traditional chocolate drinks, contain more caffeine than *forasteros*.[535] One might assume that varieties of psychoactive plants are appreciated on the basis of the quantity of the most potent psychoactive compound they contain, as seems to be the case with Cacao, where the higher-caffeine *criollo* is preferred to *forastero*. But this is often not the case; khat (*Catha edulis*) chewers from Somalia favour tender green-leafed khat over the stronger, higher-cathinone water-stressed "red" varieties; South American coca leaf aficionados prefer the lower-cocaine Peruvian *Erythrolylum novogranatense* to the Bolivian *Erythroxylum coca*; in Fiji and Vanuatu, milder but more pleasurable varietals of kava kava (*Piper methysticum*) are preferred to super-strong, high-kavalactone types such as the "tudei" cultivar (so-called because it knocks users out for two days); and in China and Japan, green, white, or fermented *pu-erh* teas (*Camellia sinensis*) may be preferred to black tea varieties, with variable levels of caffeine. In many cases the more esteemed varieties often contain lower levels of the so-called principal active constituents, but higher levels of other constituents which modify the drug's action—such preferences are dictated by perceived quality of effects, flavour, and tradition, rather than "strength" of stimulation, as measured by one compound only.

Xanthine alkaloids act as "positive reinforcers", meaning that they increase taste preferences for foods or beverages which contain them,[536] and caffeine is the most potent of the three. Even though it's often assumed that Cacao products, such as cocoa or chocolate, are not strongly stimulating, even 12.5mg of caffeine from only 8g Cacao, the amount found in a 25g bar of milk chocolate, has been shown to noticeably affect human behaviour.[537] Caffeine can increase anxiety, and actually reduces blood flow to the brain up to 30%, while simultaneously increasing brain activity. Despite this, longer-term low caffeine intake has been linked to reduced incidence of depression, and adaptation to its use means caffeine habitués move around *less* than those who don't use it at all. Caffeine levels peak in the bloodstream approximately thirty minutes after ingestion, and its stimulating effects are blunted by sugar.[538] Caffeine habituation also produces a well-known withdrawal syndrome on breaking the habit, with headache, lethargy, and low mood which can last for up to two weeks unless caffeine is consumed again.

At 1.2% of the seed's weight, *theobromine* is the most plentiful alkaloid in Cacao. It's also produced in the body as a breakdown product of caffeine. Theobromine is a stimulant, but people's sensitivity to it varies much more than with caffeine; it may even decrease caffeine's stimulating properties, although it makes no difference to caffeine's effect on mood.[539] Theobromine's effects on the heart (increasing the rate and force of the pulse) and the kidneys (increasing urination) are stronger than its effects on the brain, and it dose-dependently increases heart rate.[540] It also has the interesting property of strengthening tooth enamel.[541] Theobromine weakens some cancer cells—most strikingly, a highly aggressive form of brain cancer called glioblastoma—and helps to protect blood vessels.[542] In this regard, its actions complement those of the polyphenols in Cacao. However, high doses of theobromine can also damage the testes and inhibit sperm production, and may suppress immune function;[543] high intakes have been linked to prostate cancer in older men.[544] Theobromine also reacts with copper to produce cell-damaging free radicals.[545] Although Cacao's highly antioxidant, cell-protecting polyphenols may reverse and offset these effects, high intakes of cocoa powder (5% of the diet) have been shown to cause fertility problems in male rats,[546] so this issue should not be ignored. Like the flavanols, theobromine levels peak in the bloodstream approximately two hours after ingesting Cacao.

The third sister xanthine alkaloid to caffeine's Diana Ross is *theophylline*, comprising 0.4% of the seed. Theophylline is more stimulating than theobromine, but less so than caffeine. It does have a few unique effects though—it reduces coughing, dilates the airways, and increases the anti-inflammatory potency of steroid drugs,[547] so it's sometimes used as a medicinal drug in the treatment of asthma. It also dilates the blood vessels in the heart.[548] It has some anti-cancer effects in the lab, which may not translate to real life, but it has been shown to increase the potency of the chemotherapy drug Doxorubicin.[549] Incorporating Cacao or tea (both of which plant-drugs contain theophylline) into the diet while undergoing Doxorubicin-containing chemotherapy treatments or implementing cancer prevention strategies may be a good idea in general, as discussed later in this chapter.

Finally, there is a sprinkling of trace alkaloidal compounds in Cacao, each comprising a fraction of a percentage of the seed. Many of these trace compounds are produced by microbial action during fermentation, or by roasting the seeds, and may be found in other aged, fermented, or roasted foods, such as cheese or coffee. The quantity is small, but tiny doses don't always mean tiny results—if the compounds make it into the brain, or combine their effects with other chemicals, or build up over time, their effects can be disproportionate. These trace alkaloids are shown in Figure 5, below, as the amount found in a 40g serving of Cacao. The doses really are miniscule: to give a sense of scale, a 1mg dose is smaller than a grain of fine

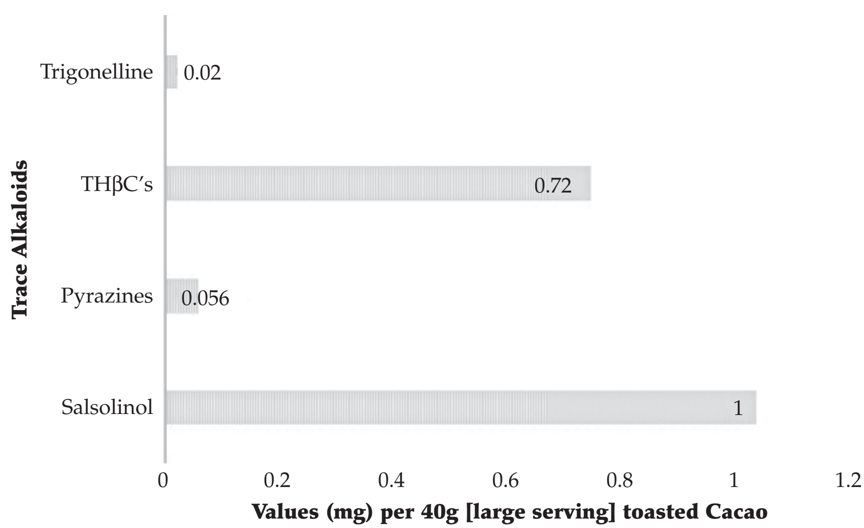

Figure 5. Trace alkaloids in toasted *Theobroma Cacao* seeds.

sand. Although, it should be noted that the strength of the individual chemicals is of enormous importance: 1mg of LSD, for example, is extremely potent.

The most plentiful of these trace alkaloids is *salsolinol*, amounting to 1mg in every 40g of Salsolinol is a trace alkaloid found in small but appreciable amounts in fermented Cacao seed (and presumably less in partially fermented varieties, such as Cacao *lavado*). Salsolinol is produced by microbes during fermentation of the seeds, and is also present in white wine and some aged cheeses, such as emmenthal.[550] Salsolinol easily crosses into the brain from the bloodstream, and has been noted to build up in nerve cells in the brain, so may have cumulative effects. It inhibits the breakdown of stimulating brain chemicals such as dopamine and noradrenaline (norepinephrine), and greatly enhances the release of the stimulating brain chemical glutamate (of which more shortly). Salsolinol is also manufactured by dopamine-releasing cells in the brain when there are high levels of ketones or aldehydes in the bloodstream, as may occur with carbohydrate-restricted diets, fasting or starvation, alcoholism, and diabetes.

Salsolinol strongly activates dopamine-releasing nerve cells in an area of the brain which plays a role in habituation and addiction,[551] so it's possible that the weak habit-reinforcing properties of caffeine may be shored up by the addition of salsolinol to Cacao's alkaloid cocktail. Interestingly, salsolinol's effects on dopamine-producing cells are strongest at very low concentrations, and taper off as the dose increases,[552] and it has been shown to accumulate in the same cells. Salsolinol may also reduce the release of endorphins (opioids) in the brain over time, causing a gradual anhedonia or loss of pleasure, as in chronic alcoholism.[553] But in the presence of endorphins or opiates, salsolinol may enhance the release of a hormone called *prolactin*,[554] which induces lactation in breastfeeding women (from the Latin *pro lactis*, "for milk"), and has a complex role to play as a brain messenger hormone in social bonding.

It's currently not possible to know exactly how much salsolinol contributes to Cacao's physical and mental effects—especially as the mental effects have, so far, only been crudely studied (as we will see in Chapter 5). Given that salsolinol is found in other non-mind-altering foods such as sardines, we may assume it has little relevance. However, we know that it has stronger effects at lower concentrations, and that it makes its way into the brain. We also know that other compounds in Cacao affect dopamine and opiate release at specific sites in the brain (polyphenols, xanthines, and other trace constituents). This means that the small but measurable quantity of salsolinol in each dose of Cacao could hypothetically be contributing to the effects of the whole drug by subtly modulating the action of other constituents, especially over time, as it builds up in dopamine-releasing cells. In the presence of heavy metals, however, salsolinol is converted into a toxic compound which damages these same dopamine-producing cells, and has been linked to the movement disorder, Parkinson's disease.[555] This issue will be further discussed in Chapter 7.

The next alkaloidal supporting cast members worthy of mention are the *tetrahydro-beta-carboline* alkaloids, or THβCs, and *trigonelline*. Like salsolinol, THβCs are products of fermentation, occur in many other foods, and can be manufactured in the human brain. Also like salsolinol, THβCs have been found to strengthen opiate and alcohol dependency in primates and rats in lab experiments,[556] activating dopamine and opiate signals in the brain,[557] and several THβCs inhibit the breakdown of the "happy" brain chemical serotonin, although the precise activities of the THβCs in Cacao are unknown. Presumably the THβCs and salsolinol act on the same brain circuitry controlling motivation and habit formation. So although present in very small quantities, these compounds could be acting in tandem to modify Cacao's effect on the brain. Closely related compounds called beta-carbolines are known to be strongly psychoactive, and some THβCs may be converted into beta-carbolines following ingestion, although this is currently uncertain.

Beta-carbolines are also found in coffee beans (another fermented, caffeine-containing seed)—but the types and quantity of THβCs per serving is different (see Table 2, below). Many THβCs are known to activate areas of the brain associated with pain relief and psychedelic responses. *Trigonelline* is present in Cacao at very low levels, and is produced from ingested niacin (vitamin B3, also found in Cacao seeds), and helps lower cholesterol and blood sugar. It also ferries the mood-elevating compound phenethylamine directly into the brain—on which subject, more to come …

Table 2. Relative beta-carboline and THβC alkaloid content in coffee and Cacao

β-Carbolines in toasted Cacao:		*β-Carbolines in roasted coffee beans:*	
Absolute:	Large serving size (40g prepared beans in approx. 60ml water)	Absolute:	Large serving size (Grande size coffee = 16oz)
0.87–7.86mcg/g beans	0.03–0.72mg	0.21mg/L prepared coffee	≤ 0.1mg
Including: • 6-Hydroxy-1-methyl-1,2,3,4-tetrahydro-β-carboline • 1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid • 1*S*,3*S*-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid • 1*R*,3*S*-1-methyl-1,2,3,4-tetrahydro-β-carboline-3-carboxylic acid • 1-methyl-1,2,3,4-tetrahydro-β-carboline		Including: • 9H-β-carboline (Norharman) • 7-Methoxy-1-methyl-9H-pyrido [3,4]-β-carboline (Harman)	

Provisioning: proteins, amino acids, and derivatives

Proteins and related compounds (see Figure 6 below) comprise around 11% of the fermented, toasted and dried seeds. Some of Cacao's proteins do have interesting anti-tumour activity in lab experiments,[558] although whether this translates to similar action in the human body is unknown. The proteins and their constituent amino acids—the bricks from which proteins are made—mainly have nutritional value, forming the building blocks for tissue and hormones and other materials the body needs to function. If free amino acids are like individual Lego® bricks, proteins are like large structures made of Lego®. The ratio of free amino acids in any food can 'push' the body towards greater production of particular proteins and compounds, much as an excess of yellow Lego® bricks and relatively few red, blue, or green ones will result in the finished Lego® projects being mostly yellow.

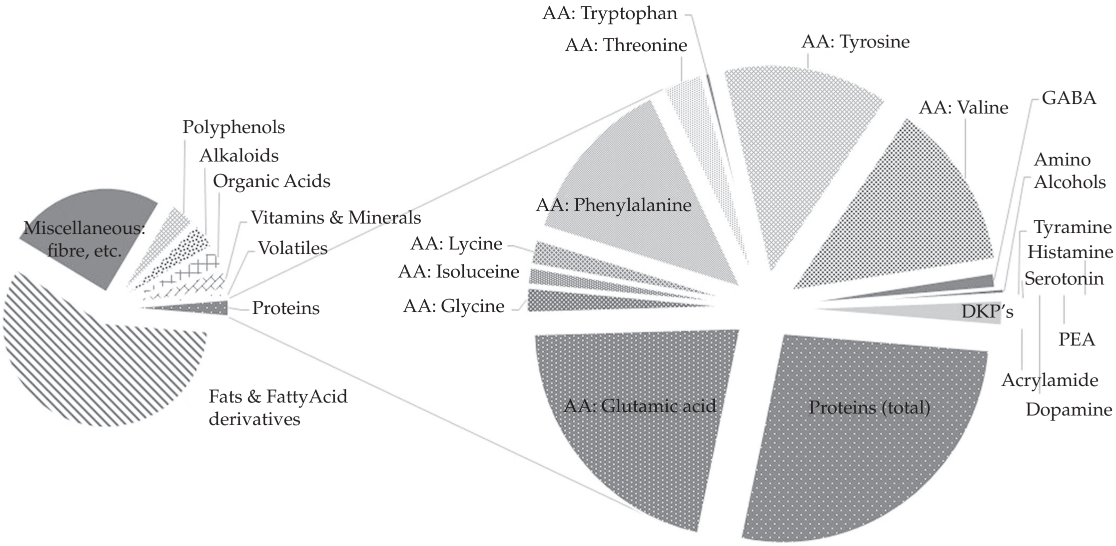

Figure 6. Breakdown of amine-based compounds in *Theobroma Cacao* seeds.

Cacao's prinicpal amino acids are *glutamic acid*, *phenylalanine*, *tyrosine*, and *valine*. Interestingly, three of these are building blocks for stimulating brain chemicals or 'neurotransmitters': glutamic acid is used to make glutamate, a common, stimulating neurotransmitter; phenylalanine is used to make the mood-raising nuerotransmitter phenylethylamine, and is converted into tyrosine if need be. Tyrosine is used to make the amines dopamine, adrenaline (epinephrine), and noradrenaline (see below). Of the four amino acids, valine and phenylalanine are essential—they can't be manufactured in the body, and have to be eaten—and Cacao contains a very high level of phenylalanine, in particular. In other words, the cocktail of amino acids in Cacao is particularly suited to the creation of stimulating and mood-raising compounds.

Amino acids themselves are made up of *amines*, many of which are used as chemical messengers in the brain. These include *dopamine*, *serotonin*, *tyramine*, *phenethylamine [PEA]*, and *histamine*. Their effect when eaten all mixed together in food is thought to be negligible, although their relative quantities in a food or drug, and the co-presence of other compounds can affect how they are absorbed and distributed in the body and increase their pharmacological potency. Mood-raising serotonin and stimulating, inflammatory histamine in Cacao are present at very low levels relative to the other amines, although Cacao is quite high in histamine in comparison with other foods. As a result of both its histamine content and having the capacity to promote histamine release, Cacao is a known trigger of nettle rash or *urticaria* in some people,[559] a condition where itching and heat in the skin can occur spontaneously. The condition is named after *Urtica* plant species, commonly known as nettles, as nettle stings contain a cocktail of chemicals including histamine and serotonin. Most people can eat chocolate without experiencing this unpleasant side effect, but it's possible that Cacao's histamine content may contribute in some small way to its stimulating effects.

Tyramine, dopamine, and phenethylamine (PEA) are broken down in the body by enzymes—naturally occurring catalysts—called monoamine oxidases. When tyramine-containing foods are eaten with compounds known as monoamine oxidase inhibitors (MAOIs), which have the property of blocking monoamine oxidase, even a low dose of 6–10mg tyramine can cause unpleasant flushing, vomiting, and high blood pressure. Several compounds in Cacao inhibit this type of enzyme, which could allow these amines to build up, and, as noted above, the trigonelline in Cacao can ship PEA directly into the central nervous system (the brain and spinal cord). Tyramine is also found in hard cheeses and some wines, and because tyramine intake is a known migraine trigger, its presence in these foods makes them a risk factor for migraine headaches. It's interesting to note that there is just over 4mg tyramine in a large 60g dose of Cacao, and when this dose is exceeded Cacao starts to produce uncomfortable symptoms such as headache, nausea, and vomiting in some individuals, effects which closely resemble a tyramine overdose.

Even more tellingly, it's been noted that low tissue concentrations of PEA increase the motivational and excitatory (stimulating) effects of dopamine and other stimulating chemicals in the brain.[560] Both tyramine and PEA act on specific receptors in the brain called trace amine associated receptors or TAARs. TAAR activation is strongly linked to the effects of several mind-altering drugs such as amphetamine ("speed") and MDMA ("ecstasy")—an intriguing link.[561] Tyramine and PEA have been described as "neuromodulators"—they have no effect on their own, but modify the effects of other brain chemicals on mood, perception, and behaviour.[562] Even though these compounds are found at infinitesimal dose levels in Cacao, it appears that these trace compounds may make a difference, after all, despite being relatively insignificant in potency and quantity. A secretary equipped with a gun and the correct access keys could assassinate a powerful dictator, where an entire army may fail: profound results are not always dependent on power or number, but can result from being given access to the right areas. The issue of Cacao's possible effects on TAARs will be discussed more thoroughly in Chapter 5.

Cacao contains a small amount of *gamma-amino butyric acid* (GABA), which, like tyramine, is also manufactured from glutamate. GABA has anti-anxiety and sedative properties in adults, although in children's brains it acts as a stimulant. GABA has some activity when taken orally, and can make it into the brain, so it's quite possible that the GABA found in Cacao contributes to its overall effects, particularly as it's present in small but appreciable doses.[563] Some compounds called *amino alcohols* are also present, and these include *anandamide*, which reduces pain, anxiety, and fear, as well as promoting weight gain and controlling milk production during breastfeeding.[564] Anandamide occurs naturally in the human brain, and binds to cannabinoid receptors—it's the natural substance which is mimicked by compounds from *Cannabis* plants, and is often referred to as an *endocannabinoid* (the prefix *endo-* comes from a Greek root word meaning "within"). Anandamide is normally broken down very quickly after ingestion, so it has been suggested that it has no relevance to the effect of Cacao or chocolate on mood or cognition. But it's active at tiny doses,[565] and the other amino alcohols in Cacao, the *n-acylethanolamines*, inhibit its breakdown at very low levels.[566] A fat-based substance called phosphatidylethanolamine in Cacao seeds is also a precursor of anandamide. So, again, the combined effect of these trace substances may be greater than their quantity might suggest. Cacao's history of use to allay fear and anxiety, gain weight, and promote lactation all suggest that GABA and the amino alcohols may contribute to the seeds' activity, despite their low profile.

The *diketopiperazines* (DKPs) are produced during fermentation and toasting of the seeds, so they are found in traditional Cacao beverages and mass-produced eating chocolate, but aren't present in unfermented and uncooked "raw chocolate". They have a bitter taste which contributes to Cacao's overall flavour, and very little is known of their physiological effects, except that they can get into the brain.[567] There are many types of DKP, and some varieties protect nerve cells from damage, inhibit cancer cell growth, lower blood sugar, or inhibit the growth of harmful microbes; but precisely what the DKPs in Cacao do once ingested has yet to be determined. Some of the DKPs may reduce morphine dependency and withdrawal, or alter sensitivity to hormones.[568] Like the THβC alkaloids, also produced during fermentation and heating, a few of the DKPs in Cacao are also found in coffee beans.

Acrylamide is a cancer-causing toxin produced during high-temperature roasting of the beans, although its content in Cacao is low and decreases with storage.[569] The quantity of acrylamide in cocoa powder is up to thirty times higher than in Cacao seeds or cocoa mass, owing to the extra processing—perhaps another argument for adopting traditional Cacao beverages over industrially processed, low-quality cocoa. See Figure 7 below for a graphic representation of the quantity of various trace amines in a 40g serving of Cacao.

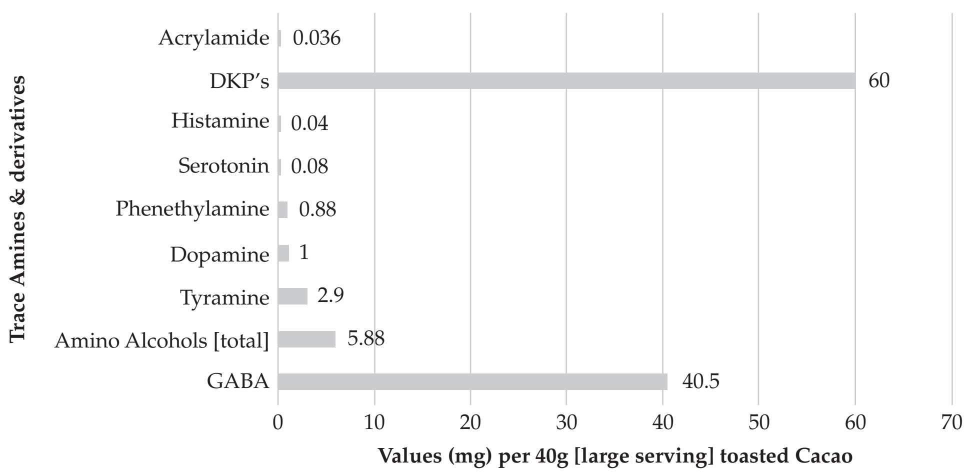

Figure 7. Trace amines and derivatives in toasted *Theobroma Cacao* seeds.

Vitalising: vitamins, minerals, and essential oil

Cacao contains significant levels of the dietary minerals *copper* and *magnesium*. A single 40g serving of Cacao contains more than the entire daily nutritional requirement of copper for an adult. Copper is used to convert dopamine to noradrenaline, a stimulating and euphoriant brain chemical, although an excess of copper may build up and eventually cause damage to dopamine-producing nerve cells, which can result in the movement disorder known as Parkinson's disease. Subjects with depression often have relatively high blood copper levels,[570] and excessive copper intake is known to be detrimental to mood regulation. On the other hand, adequate copper intake is important for dietary iron absorption, and Cacao is a high-iron plant too. So Cacao's copper content may be beneficial for anaemic persons or those with a low-copper diet, but may become harmful over time if the diet is otherwise high in this mineral.

Adequate dietary magnesium contributes to preventing health problems such as high blood pressure, migraines, fatigue, and cramps, and reduces the risk of heart disease and stroke.[571] Very low magnesium levels are associated with depression, and dietary sources of this mineral are important for people prone to mood disorders; supplementation with magnesium has rapidly reversed some cases of major depressive disorder.[572] So here's another rationale for Cacao's heart-protective properties and history of use as a mood-altering food-drug. Cacao is also relatively rich in the trace mineral *manganese*, which is incorporated into many enzymes used in various chemical reactions throughout the body, one of which (superoxide dismutase, or SOD) has the important function of preventing free radical damage. The manganese in Cacao also has a supportive role in maintaining good blood sugar control,[573] which may bolster the hypoglycaemic activity of Cacao's polyphenols. As with copper, excess manganese can become toxic to dopamine-producing cells in the brain by increasing oxidation and overstimulating them, giving rise to Parkinson's disease and other cognitive or behavioural problems.

The *criollo* variety of Cacao is "highly aromatic" and considered to have the best flavour.[574] This suggests that it may have a higher volatile oil (aka essential oil) content. Being very small, airborne molecules, volatile compounds are generally inhaled and sometimes influence brain function directly, via a signalling pathway that links smell to the reactive, emotional, and instinctual part of our brain. This is one reason why specific smells can strongly evoke certain feelings and memories. The molecules in Cacao's complex aroma individually resemble burnt meat, peanuts, maple syrup, cinnamon, coconut, sweat, sulphur, and pepper, and their complex blend produces the uniquely evocative aroma of chocolate. Several of the compounds in Cacao's perfume may directly affect brain cells. Three are known to be stimulating and dopamine-increasing (3-methylbutanal, hexanal, and phenylacetaldehyde). Others inhibit the growth of various microorganisms such as bacteria and yeast, which may play a role in the long shelf life of Cacao products and the seeds' traditional use for treating diarrhoea (dimethyl trisulphide, 2-phenylethanol, nonanal, and ethyl cinnamate). Two compounds in the essential oil, 2–4 nonadienal and ethyl cinnamate, also reduced cancerous transformation of skin cells stimulated by ultraviolet light and inhibited melanoma growth,[575] which may infer a potential use for Cacao as topical after-sun skin treatment—particularly with the burn-healing properties of the stearic acid in cocoa butter.

The chemistry of chocolate making

During **fermentation**, *phase one* of Cacao's transformation, microbes change the flavour of Cacao—making it less astringent (dry) and more acidic (sour), and turning the white-purple beans brown and more recognisably "chocolatey" in smell and taste. Fermentation is, of course, "controlled rot". Many of humanity's favourite foods and drugs such as chocolate, cheese, coffee, wine, beer, bread, yoghurt, and soy sauce are products of deliberate decay. In Cacao's case, nature is almost given free rein: the freshly harvested beans are piled up or contained in the prescribed manner (as described in Chapter 2) and the microbes left to do as they will, for one to eight days, depending on the variety of bean and intended results, established over centuries or millennia of experience. This mess of microbial and chemical activity entails multiple complex chemical reactions. The heat and moisture of fermentation initiate seed germination, then sterilise the seeds; microbial by-products, and the changes wrought in the seed, create a slew of precursor chemicals which are further transformed by toasting to create the characteristic flavour and odour of Cacao.[576] Without at least partial fermentation, important trace compounds are omitted (see Table 3, below). The fermentative microorganisms excrete organic acids such as acetic acid (the main acid in vinegar) and alcohols, permeating the beans and dissolving cell walls.[577] Because more air gets into box-fermented beans, more aerobic bacteria proliferate, as opposed to the greater quantity of yeasts in heap fermentation. Bacteria tend to produce more acids, which gives the bean a vinegary taste, whereas yeasts produce more ethanol, which is less sour;[578] this explains why well-managed smaller heaps generate better flavours. In a sense, the fermentation of Cacao is only partial, as the microbes don't get into the beans' innards—their activity is restricted to the outer shell, but the acids and alcohols they excrete do penetrate the shell and infuse the seeds, changing their chemistry and flavour. The heat, acidity, and variable exposure to oxygen reduce many of Cacao's polyphenols into smaller, sometimes inactive components.

Table 3. Gain and loss of known compounds whose presence and quantity differs in raw, fermented, and toasted Cacao

Compounds present:		*Unfermented, dried Cacao*	*Raw, fermented, & dried Cacao*	*Fermented, dried, & toasted Cacao*
Alkaloids	Indoles [THβCs]	–	**GAIN**: Present—produced during fermentation.	NO DATA
	Pyrazines	–	–	**GAIN**: Pyrazines formed during toasting; increase with longer roasting and higher temps.
Phenolics	Procyanidins Flavan-3-ols N-phenylproanoyl-l-amino acids	Total phenolics = 6–8% dry weight of bean.	**LOSS**: occurs due to oxidation with cell wall (parenchymal) dissolution in fermentation, plus heat generation.	**LOSS:** due to heat-induced oxidation. Total phenolics = 126 pprox. 1.2% dry weight of bean. NPA ≤ 60% decrease during toasting. Longer roasting and higher temps. = greater loss.

(*Continued*)

Table 3. (Continued)

Compounds present:		*Unfermented, dried Cacao*	*Raw, fermented, & dried Cacao*	*Fermented, dried, & toasted Cacao*
Proteins, etc.	Albumin	Present. ≤ 1.5% dry weight.	**LOSS + CHANGE**: semi-fermented Cacao albumin has *in vitro* anti-tumour activity.	**LOSS**: 13% albumin loss after 42 mins toasting at 150°C; thereafter, rapid decline.
	Amino Acids	Present.	**GAIN**	**LOSS**
	Amino Alcohols	Present.	NO DATA	NO DATA
	Biogenic Amines	Present.	**GAIN—**levels increase during fermentation with proteolysis.	**LOSS—**variable, dependent on length and temp. of toasting.
	Diketopiperazines	–	**GAIN—**produced during fermentation.	**GAIN—**heat increases formation.
	Acrylamide	–	–	**GAIN:** produced during toasting proportional to temperature, but decomposes with longer toasting and in storage.
Volatile compounds		Present.	**GAIN:** new volatile compounds produced during fermentation.	**GAIN—**net gain, some loss by volatilisation and oxidation. Transformation and production of many new volatile compounds.

It's been observed that so-called Cacao *lavado* from Chiapas and Tabasco in Mexico (and used as standard in Alta Verapaz in Guatemala, though not referred to by this name), the variety of Cacao bean which is fermented for one day only before being washed and dried, has a much higher content of the "antioxidant" compound epicatechin than fully fermented seeds. Epicatechin is one of the most studied compounds in Cacao, not least because it's also thought to be one of the main "healthy" constituents in *Camellia sinensis*, the tea plant. Many of the proteins in Cacao are denatured into amino acids during fermentation, some of which are themselves disassembled into amines such as 2-PEA (phenethylamine). Many of the polyphenols and amines created by fermentation are later decreased by roasting and even further by alkalisation, if the Cacao is made into cocoa powder.[579] Fermentation also generates tiny quantities of tetrahydro-β-carbolines, diketopiperazines, and rafts of new volatile compounds, all of which contribute to the complex pharmacology and flavour of chocolate. So Cacao *lavado*, fermented for only a day, contains a higher level of polyphenols but fewer trace amines and trace alkaloids; Cacao *fermentado*, the reverse.

Phase two, **drying**, can either be done artificially (if the weather is rainy or unpredictable), or in the sun. Sun-dried beans taste best. Fresh Cacao seeds are up to 65% water[580] but after fermenting and drying, this is reduced to 6–8%.[581] Paradoxically, fermentation has antimicrobial effects; the weak acids produced during fermentation inhibit the growth of contaminants such as *Aspergillus* fungus species.[582] A few traditional chocolate drink formulas call for raw, lightly fermented beans, but they are in the distinct minority. One of the reasons for this may be hygienic—as contemporary "Cacao shaman" Keith Wilson points out, if the raw beans are laid out to dry in the sun after fermentation in many country farms in Central and South America they often get "rinsed with barnyard tea" by various domesticated animals wandering about (see Appendix C, Interview 3). Research has found that if fermenting Cacao is inoculated with *Salmonella* bacteria, the *Salmonella* count will actually continue to increase during drying, whereas if beans are exposed to *Salmonella* during drying, there was very little increase in *Salmonella* counts.[583] What this suggests (other than the advisability of not permitting microbiologists access to your fermenting Cacao beans) is that while dirty conditions during drying (Keith's "barnyard tea" scenario) may not be so critical, any exposure to microbial contaminants during the fermentation process could be disastrous—and many small producers in poorer regions have less than perfect sanitation.

Phase three is **toasting** the beans: one of the consistent features of traditional chocolate drinks, as described in Chapter 2, is that they were almost universally made from *toasted* Cacao beans. The heat kills off any remaining unsavoury microbes on the beans, so toasting is an important step in sterilising Cacao before consumption, in addition to catalysing more obvious changes in taste and savour. Toasting the beans (or industrially roasting them) lowers moisture levels even further, to 2–3% of the beans' weight,[584] also decreasing acidity levels and altering the volatile oil content, creating many new aromatic compounds, such as the diketopiperazines. It's known that theobromine forms "chemical adducts" with diketopiperazines during roasting,[585] creating new combination compounds, with as-yet unknown effects on their pharmacological properties.

The characteristic "chocolate" aroma and flavour are properly developed during toasting through a series of chemical transformations known as Maillard and Strecker reactions. Maillard reactions occur in foods when they are cooked to the point where they "brown"—heat causes intrinsic sugars to break down and react with proteins in the presence of water, generating new flavours. The brown colour of the toasted beans comes partly from compounds called melanoidins, generated from sugars and proteins in Maillard reactions.[586] The first molecules formed in Maillard reactions are referred to as "Amadori compounds", composed of free amino acids and sugars; in Cacao's case, Amadori compounds are produced from reactions between phenylalanine (which the beans contain a lot of) and fructose, which create many characteristic chocolate flavours.[587] Strecker reactions specifically refer to the formation of aldehydes (chemical compounds related to alcohol) from amino acids;[588] in fact the characteristic "roasting chocolate" smell is produced when the amino acids leuceine, threonine, and glutamine react with glucose, creating new volatile aromatic compounds, or "Cacao essential oil" as an aromatherapist would say—the distinctive fragrance or perfume of chocolate, basically. Strecker reactions are very important in Cacao processing, as they also cause the formation of trace alkaloids known as *pyrazines* which contribute significantly to chocolate flavour.

One of these pyrazines (tetrahydromethylpyrazine, or THMP) produced during roasting of Cacao seeds improves blood flow through the brain and spinal cord, reduces inflammation in blood vessel walls, and protects nerve cells from damage caused by temporary oxygen deprivation[vii] in high doses—such damage occurs in stroke, heart attack, or accidents where blood supply to cells may be interrupted. Although the amount of THMP in Cacao is very small, its properties complement those of Cacao's flavanols and procyanidins, present in much greater quantities, which have similar effects. The interesting thing is that roasting causes the formation of other pyrazines, such as trimethylpyrazine when Cacao is toasted at above 120°C, as in traditional processing methods (toasting on a *comal*), and two forms of dimethylpyrazine, created with higher-temperature cooking, associated with industrial processing to make eating chocolate and cocoa powder. Little is yet known about the pharmacology of these other pyrazine compounds produced during cooking, and what specific effects they may have in the human body after ingestion.

It's estimated that around 69% of all Cacao used in eating chocolate may be "overcooked"—being UHT (ultra-high-temperature) treated, baked in giant ovens or even smoked,[589] seriously denuding its content of polyphenols and other probable actives such as biogenic amines, and thereby greatly reducing its medicinal value. However, if the roasting temperature is kept around the 100°C (212°F) mark, it's possible to maintain 90% of Cacao's flavanols intact.[590] Optimal toasting temperatures and times for the preservation of the widest range of chemical components and best flavour have been calculated: temperatures greater than 150°C produce more of the carcinogenic product *acrylamide* and destroy more of the polyphenols, while toasting for less than forty minutes preserves the bulk of the proteins which remain after fermentation.[591] Fortunately, most chocolate manufacturers roast at temperatures from 110–140°C (230–284°F);[592] less fortunately, the roasting is usually continued for forty-five minutes to an hour. The "optimal" toasting temperature and duration for generating a good flavour profile while conserving oxidisable constituents has been calculated as twenty-three minutes at 116°C (241°F)! This time and temperature minimises acrylamide production, preserves polyphenols, and generates flavoursome (and biochemically active) pyrazines.[593]

In general, research indicates that lower temperatures and shorter roasting times are best for optimal Cacao chemistry—another reason for respecting the traditional method of toasting the seeds on open-air clay *comales* at lower temperatures, not roasting them by the kilo in huge metal ovens. It must be remarked that in present-day Mexico and Guatemala there is huge variation in the degree to which Cacao is toasted. I witnessed relatively brief toasting of beans with a low flame on clay *comales* for preparation of *tejate* in Oaxaca (see Chapter 8 for recipe); I also witnessed Cacao being charred to a coffee-like finish in smoky huts in Guatemala. Production quality was strongly influenced by individual preferences. Whether this was the case five hundred or a thousand years ago in the same region before the arrival of Europeans is open to speculation.

[vii] Ischaemia-reperfusion injury.

Preparing the toasted beans for making traditional Cacao beverages also causes chemical changes to take place, altering both flavour and pharmacology. This is even truer for "candy bar" chocolate, owing to the additional processes required to produce it. *Phase four*, **shelling** the beans, involves no notable pharmacological changes, but reduces the quantity of lignin—the major component of wood—in the final product, as well as the quantity of carcinogenic acrylamide in the burnt shell casings. The differing methods employed in *phase five*, **grinding** the beans to make chocolate, also affect the final product's chemistry and taste. Grinding can involve either shearing or pounding. The favoured industrial and traditional method is shearing, wherein the beans are crushed between two sliding surfaces. For industrial production of chocolate, disc mills are used, which sandwich the seeds between one rotating surface and another fixed one, breaking the seeds up most effectively. This is akin to the traditional Mesoamerican method of grinding the beans on a *metate*, or the European practice of grinding grains in a round mill. The other, less favoured method is to pulverise the beans with repeated impacts, as with mechanised pistons or "impact mills" where the nibs are pounded to a paste by hammer-pins, or by hand in a mortar and pestle, known as a *molcajete* in contemporary Latin America. In both scenarios, heat generated by the friction causes the fat in the beans to liquefy and coat the diminishing particles of solids as they are pulverised, transforming the solid beans into unadulterated cocoa liquor.[594]

Using a mortar and pestle is much slower work than grinding on a *metate*, and produces a slightly inferior drinking chocolate, as does simply grinding the beans in a machine (called a "melangeur") using granite rollers. One reason for this may be that drawing the fresh cocoa liquor up and down the flat surface of a hot *metate*, repeatedly spreading a film of chocolate over a broader surface area, allows more of the sour-tasting organic acids produced during fermentation to evaporate, thereby mellowing the flavour. By contrast, grinding the liquid in a bowl or even mixing large volumes in a machine will not allow as much acid to vaporise and escape.

Cocoa liquor consists of tiny particles of plant fibre such as cellulose and lignin suspended in liquid cocoa butter, and is very prone to pick up odours.[595] So, as per traditional recommendations (see Chapter 2), any aromatic spices such as vanilla or allspice should be added to chocolate when it is ground, before it's made into a drink or allowed to cool and solidify. Solid chocolate (whether factory-made slab for eating, or Cacao discs and tablets for making drinks) retains some of this odour-absorbing tendency, which is one reason why chocolate should never be kept in the fridge unless it's stored in an odourless, airtight container. One might surmise that the process of grinding Cacao beans must inevitably cause some decline in the quantity of active compounds in the cocoa liquor. The repeated back and forth motion involved in grinding beans on a *metate*, for example, must expose some polyphenols in the film of warm chocolate to oxygen, with which they may react, and also inevitably cause some volatile oils to disperse. So this would have the effect of making the flavour milder and more pleasant, by virtue of liberating some of the acids, but may simultaneously diminish some of the pharmacological effects of the polyphenols.

The first few hours of industrial conching cause a steep decline in complex polyphenols, which break up into smaller, still-active flavonols, as the continuously moving surface of the cocoa liquor comes into contact with the air, and presumably air is also beaten into the mixture. The amount of volatile compounds which can be detected in the air above a conche declines by over 80% over those first few hours.[596] During conching the cocoa liquor's moisture content is reduced by a further 30%, and several flavour compounds have been noted to diminish during this operation,[597] modifying the chocolate aroma and its pharmacological profile. Less-intensive traditional manual processing of Cacao (such as toasting on a *comal* and grinding on a *metate*) is likely to be less detrimental to the polyphenol content than industrial conching.

But even industrial processing produces relatively little change in the overall flavonoid content of the cocoa liquor unless the fat has been removed—as occurs in the production of "Dutched" cocoa powder, for instance. Dutching may help to mix cocoa powder with water as the alkaline potassium carbonate added to the beans *saponifies* fats in the seed, in other words it produces soapy compounds, in the same way that lye added to fat makes soap. Too much potassium salt causes the cocoa to taste soapy;[598] just right, and it will help residual fats in the powdered seed mix with water, and prevent clumping. Pharmaceutically speaking, though, Dutching has a high cost: the reason that Dutched cocoa is darker in colour and milder in flavour than Cacao, "natural" cocoa, or cocoa liquor, is that another 10–30% of the flavanols are lost to oxidation during the alkalising process, diminishing the flavour and potency of the finished product. It seems that the high fat content of Cacao—the "cocoa butter"—protects many compounds in the seeds from exposure to the air, and therefore to oxidation, during grinding and conching. Cocoa powder still contains around 12% to 22% fat,[599] but because some of that fat is saponified, the lipids aren't an effective barrier against water any more, and can no longer protect delicate compounds from oxidative chemical reactions. Only baked chocolate goods have lower medicinal potency than cocoa powder—so chocolate cake should not be excused as medicine, at least not on pharmacological grounds, as most of the remaining flavanols will be lost on baking. Its value as a comfort food, however, may be a different matter.

The key "ingredients" for deterioration in Cacao's flavanol content are high temperatures, reduced fat content, exposure of dry and de-fatted seed matter to air, and the presence or addition of moisture. All these elements are maximised in the production of industrial cocoa powder; the "alkalisation" step involves water, with the result that processed cocoa has very low flavanol content, eating chocolate has variable flavanol content, and traditional chocolate drinks made from comal-toasted Cacao have high flavanol content. "Raw chocolate" products made from untoasted Cacao potentially have the highest flavanol content of all—so long as they are made from the whole bean, not de-fatted Cacao bean powder, which many of them are; in the latter case, the flavanols will slowly oxidise with exposure to air. But raw chocolate products lack some of the other molecules produced during toasting such as the pyrazines and volatile compounds, to say nothing of the increased risk of unwelcome microbial guests as a consequence of omitting the cooking process (see above re contamination). Unfermented raw beans also lack the biogenic amines, including the much-discussed PEA, and several interesting trace psychoactive alkaloids and amine-based compounds such as the THβCs and DKPs, which may be crucial for enhanced psychoactive and medicinal effects. Fermented but uncooked Cacao has the highest levels of amines, but lower levels of pyrazines, DKPs, and volatile oils than toasted Cacao (see Table 3 below).

Phase six, **setting** the Cacao, that is, allowing the cocoa liquor to solidify for storage, is optional in traditional chocolate manufacture, and depends on whether the Cacao-based beverage is to be drunk immediately or later on. In this case, no sugar or extra fat is added, so there are no complicated processes involved. "Bloom", the bane of the chocolatier's existence, occurs when cocoa liquor melts and resets without temperature control, and is caused by the fat having separated out owing to the different "crystallisation forms" cocoa butter can take. Cocoa butter set at lower temperatures has an "unstable" structure, but if set at temperatures of around 30–34° Celsius (86–93.2°F), then the crystalline structure of the solidified fat will be stable.[600] If the cooling process isn't carefully controlled by tempering, or if you keep chocolate somewhere it will be exposed to heat then cool down again (e.g., near a sunny window, or the stove), still-liquid fat is squeezed out of the solidifying matrix of cooling cocoa butter onto the surface of the chocolate, giving your chocolate bar eczema. Bloom is a non-issue for traditional forms of drinking chocolate, as it is destined to be dissolved in hot water before consumption, so uniform texture and colouration makes no difference.

The cooled and set Cacao is now ready to make into drinks. Many books have reported the difficulty of getting solid chocolate to dissolve in hot water as a reason why traditional whole-bean drinking chocolate fell from favour, claiming that the high fat content of the bean meant such drinks were tricky to prepare, and likely to separate. But this is a fallacy: as long as drinking chocolate is made from well-ground whole beans—"well ground" meaning worked to the consistency of a smooth liquid before setting—they will readily and easily disperse when beaten or whisked into hot water. (This isn't true of ordinary "candy bar" eating chocolate, whose added fat content is too high to allow it to disperse easily in hot water.) One reason for this may be Cacao's content of a small amount of lecithin, a natural emulsifier.[601]

Chocolate, the superdrug?

1. Chocolate hearts, sweet blood

The native Kuna of the San Blas islands in Panama are accustomed to drinking five or more cups of traditional, whole-bean drinking chocolate every day—around forty cups of real, full-potency Cacao-based drinks every week. Being made only from toasted Cacao, water, banana, sugar, and spices, these beverages are naturally flavanol-rich; it's estimated that the average Kuna adult consumes about 900mg of Cacao polyphenols per day,[602] equivalent to 22.5–75g (¾–2⅔oz) of high quality Cacao seed. This is approximately the same as 75–150g (2⅔–5oz) dark chocolate per day, but without the added fat, and less highly processed so undoubtedly containing more polyphenols, and probably with a better flavour to activity ratio too. The Kuna living in San Blas experience very little age-related high blood pressure, circulatory disease, or type 2 diabetes, but when they move to other regions and abandon their traditional diet and the copious quantities of ultra-high quality drinking chocolate that entails, these migrated Kuna acquire the same levels of diabetes and cardiovascular disease as any other average city-dwelling, Western diet-consuming population.

This observation is highly relevant because cardiovascular disease (CVD)—including heart attack and stroke—is the main cause of death in the so-called developed world, killing an estimated 17 million people every year.[603] Which makes it interesting that there is now a growing body of clinical research suggesting that Cacao is a highly effective preventive remedy for these disorders. Dark chocolate slightly lowers blood pressure and beneficially affects cholesterol profiles, marginally raising HDL and lowering LDL and total cholesterol, indicating a small reduction in the risk of heart attack or stroke.[604] Far more significant is the effect of Cacao on the "vascular endothelium", the inner lining of blood vessels, and on platelets, components of the blood which are central to the clotting process. The flavanols in Cacao increase nitric oxide production in the vascular endothelium, dilating blood vessels and increasing blood flow throughout the body. The polyphenols also reduce platelet aggregation and clot formation, and stimulate *angiogenesis*—the growth of new blood vessels.[605] Essentially, Cacao appears to be a haemodynamic marvel, simultaneously reducing almost every risk factor for cardiovascular disease: it dilates narrowed blood vessels, decreases the tendency to clot, reduces inflammation in the lining of blood vessels, lowers levels of blood lipids which can accumulate on damaged artery walls, stabilises damaged red blood cells, strengthens the heartbeat, reduces blood pressure, and increases the rate of blood vessel repair. (See Appendix A for full details of the studies conducted on Cacao and chocolate.)

A meta-analysis is a type of study which rounds up all previous studies on the same subjects, filters out the ones that weren't done to a high enough standard or where the results may be inaccurate or biased, and works out what the sum total of the evidence so far is saying. It should be no surprise that a 2011 meta-analysis of Cacao's usefulness for preventing CVD concluded that people who eat the most chocolate were 37% less likely to have a heart attack and 29% less likely to have a stroke than people who ate little or no chocolate, *no matter what else they did*; smokers, the obese, people who didn't exercise, people who ate only fried food—they all had similar reduction of relative risk if they ate more chocolate.[606] This extraordinary finding is derived from several large surveys: in the US a Boston study which used questionnaires and heart scans (cardiac computerised tomography) to assess 2217 participants found an inverse association between frequency of chocolate consumption and coronary artery atherosclerosis, with the lowest risk of arterial disease for those who consumed chocolate two or more times per week.[607] In a separate, questionnaire-only study with 4970 participants from the same population, frequency of chocolate consumption was also found to reduce risk of coronary heart disease (CHD) even more significantly. The greatest reduction occurred for those who consumed chocolate five times or more each week (a 57% relative risk reduction compared to non-consumers); eating chocolate one to four times a week reduced CHD risk by 26%, but those who consumed chocolate only one to three times each month had the same risk as non-consumers.

Interestingly, the latter study also showed that consuming *non-chocolate* candy five times or more each week was associated with a 49% *higher* relative risk of CHD—in other words, higher added dietary sugar intake clearly increased the risk of developing heart disease, if the sugar was not mixed with Cacao in the form of chocolate.[608] This makes sense, given the observation that carbohydrates increase the absorption of Cacao's polyphenols. In both of the Boston studies great care was taken to get a clear picture by adjusting for other factors which could have affected the result, such as smoking, alcohol intake, exercise, calorie intake, BMI, fruit and vegetable intake, age, sex, and education. Another study from Germany suggests that the protective effects of chocolate may be even stronger against stroke than heart and arterial disease. This eight year population study with 19,357 participants showed that the people with the highest levels of chocolate consumption had a 49% relative risk reduction for heart attack and stroke put together, with slightly stronger protective effects against stroke. Most interestingly, the group with the lowest risk—the most avid consumers of chocolate—also had the lowest vegetable intake![609]

To illustrate these results: say forty-two in every 1000 UK residents have CHD: the UK population is 63.7 million, and 2.7 million UK residents have CHD (as of August 2013): a staggering 4% of the adult population with confirmed heart disease. If all adult UK residents consumed dark chocolate five times or more each week, then—if these figures bear out—only eighteen in every thousand UK residents (1.8% of the population) may go on to develop CHD. This is a massive difference; across the whole population approximately 1.5 million fewer UK residents could have CHD. Even if all UK residents were to eat only one to four "servings" of proper (dark, high Cacao-content, preferably 80% or higher) chocolate a week, CHD prevalence could be reduced from 2.7 million to 2 million, meaning that 700,000 fewer people could be living with this severe health problem.

In 2009, the total healthcare costs for CHD in the UK (primary care, outpatient care, emergency care, inpatient care, and medications combined) cost the NHS approximately £1.8 *billion* (approximately US$2.4 billion).[610] Not everybody needs a chocolate prescription to cut these numbers: if people at higher risk were targeted, such as those with a family history of CVD, high blood pressure, high cholesterol, and so on, then by the simple expedient of encouraging everybody in higher risk groups to eat *at least one serving of real dark chocolate every week*, UK healthcare costs could potentially be reduced by up to £468 million for coronary heart disease *alone*. If people at high risk of developing CVD (family history, smoking, no exercise, etc.) ate quality chocolate at least five times a week, the cost could be more than halved, a national saving of over £1 billion effected by chocolate.

One might ask, if this is the case, then why does the UK—one of the world's highest chocolate consumers—have such a high prevalence of CVD? The answers are: quality, distribution, and sugar. Put simply, the people who most need good chocolate (in terms of their dietary and lifestyle risk factors) are not the ones who are eating it; and the "chocolate" they are eating may have only a superficial acquaintance with Cacao. Many of the "chocolate bars" or "chocolate-flavoured" products which crowd the confectionery aisles of supermarkets and the counters of petrol stations are over-advertised pretenders to the name, so loaded with sugar and cholesterol-raising fats that they're more likely to increase the level of CVD risk. Which may explain the bizarre, ironic inanity of a recurrent British Heart Foundation campaign, urging people to "De-Chox"—to be sponsored to give up eating chocolate, *for the sake of their heart health*, to raise money for heart disease research and treatment. The campaign produces mugs and badges with phrases like "balls to chocolate", and "give chocolate the finger".[611] This could be intended to reduce dietary intakes of added sugar and saturated or trans-fats, assuming that most "chocolate" is just cake and low-Cacao confectionery, and that chocolate eaters are likely to have other, less healthy habits, too. But as we have seen, eating real chocolate reduces risk of CVD even when other lifestyle risk factors are present. The campaign is appallingly wrong-headed, demonising the only type of confectionery which has a protective effect!

If every UK resident consumed *only* non-chocolate sweets (to which I would add soft drinks (sodas), biscuits, confectionery, etc., five times or more each week, avoiding chocolate entirely, the prevalence of CHD could *rise* to sixty-three out of every thousand UK residents (6.3%), bringing the total number of people living with heart disease up to four million, and escalating the national bill for coronary heart disease health care to £2.7 billion. To be effective, the use of chocolate for disease prevention must target the correct groups and entail sufficient consumption of high quality Cacao, while *simultaneously* replacing dietary consumption of other refined sugar-containing foods. A bog-standard "chocolate bar" comprising 25% biscuit, 75% refined sugar and fat, 4% highly refined cocoa powder and 1% added god-knows-what just won't cut it, and will—at best—do nothing to reduce CVD risk. The chocolate needed for noticeable effect is dark, rich, and strong.

So our currently high levels of CVD are the consequence of a national diet loaded with added sugar, saturated fat, and a dearth of beneficial botanical compounds. Few of the people who need it are eating enough of the right type of chocolate. Which begs the question—how would disease statistics, and the consequent healthcare costs, be affected if refined sugar was entirely removed from the UK diet, *and* people at risk of heart disease or stroke switched to consuming traditional chocolate drinks, sweetened only a little, or not at all?

What's true of chocolate and heart disease may also be true of diabetes mellitus, or chronically high and uncontrolled blood sugar. In diabetes, the pancreas either stops producing the hormone insulin (in type 1 diabetes, and—eventually—type 2 as well), or the cells become unresponsive to insulin (type 2). Insulin enables all the cells in the body to absorb glucose, which they use for fuel. If insulin isn't being produced, or the cells stop responding to it, blood sugar rises and the cells begin to starve; as Coleridge's ancient mariner said, "Water, water everywhere, nor any drop to drink"—though in diabetes mellitus it's "glucose, glucose everywhere …" Insulin also helps cells take up fats (triglycerides) and proteins, so these rise in the bloodstream too, and the consequences of all the extra sugar and fat in the blood is a gradual clogging-up of the circulatory system, with small blood vessels in the eyes, kidneys, hands, and feet gradually closing up; even larger organs, such as the liver, brain, and heart become more and more congested with fat and unable to function as well. Diabetes effectively silts up the whole body, increasing the likelihood of acute disease and early death.

The mixture of flavanols in Cacao have been shown to rapidly lower the levels of fats (triglycerides) in the blood and reduce fat production (lipogenesis) in mice at high levels of intake,[612] equivalent to around 108g whole Cacao for a human, a high dose but within the realms of possibility for daily human consumption. Human studies have substantiated these results: in several trials, high-polyphenol dark chocolate was found to improve pancreatic function and insulin sensitivity, reduce blood pressure and cholesterol, and improve arterial blood flow over periods of up to twelve weeks, in doses equivalent to an average of 80g Cacao per day.[613] More recent lab and animal research suggests that Cacao may help protect both the liver and pancreas,[614] reducing the risk of developing diabetes and fatty liver disease.

Another potentially serious medical condition which affects the circulatory system is anaemia. Technically, anaemia is a generic term which may have several different causes. The name means "without blood", and refers to symptoms caused by a reduction in the ability of red blood cells to carry oxygen around the body. It's a disease state characterised by shortness of breath, fatigue, pallor, and rapid heart rate; it can also lead to faintness, angina (chest pain brought on by exertion), pains in the legs and calves on walking, and—eventually—heart failure. Causes of anaemia may include blood loss from heavy menstruation, or low dietary iron intake. But two major types of anaemia are caused by specific inherited mutations in the genes coding for haemoglobin, the substance made from proteins and iron which resides inside red blood cells and transports oxygen around the body. These "altered haemoglobin" anaemias are thalassaemia and sickle-cell anaemia, which affect millions of people worldwide. The current prevalence of these disorders is 2.55 per 1,000 births; 56,000 children are born with thalassaemia major and 275, 000 babies are born with sickle-cell disease every year,[615] making them major health issues on a global level.

Thalassaemia is the name given to inherited disorders in which haemoglobin isn't properly formed, causing red blood cells never to mature or to die easily. Severe thalassaemia causes bone deformities, recurrent bacterial infections, leg ulcers, and gallstones, and requires blood transfusions to treat, often leading to toxic iron accumulation. In sickle-cell anaemia, red blood cells (erythrocytes) appear normal until subjected to stress such as low blood oxygenation or inflammation, at which time the mutated haemoglobin polymerises (forms long chains) and deforms the shape of the erythrocytes from blood-vessel-friendly squashy biconcave discs to pipe-clogging crescent ("sickle") shapes. The more this happens, the more inflexible the "sickled" blood cells become; they tend to pile up and block blood vessels, causing upstream tissue damage and severe pain. The "sickle-cell crisis" is usually accompanied by fever, and can present as bone, chest, liver, or kidney pain, epileptic fits, or painful, persistent erections in men (priapism). Without access to good medical treatment, sickle-cell disease usually results in reduced lifespan (death typically occurs at forty to fifty years old).

The relevance of Cacao to these diseases should be obvious: if *Theobroma cacao* can stabilise red blood cells, reduce clotting, and prevent inflammation in the walls of blood vessels while dilating them at the same time, might it not help alleviate sickle-cell disease, reducing the possibility of a crisis? *Theobroma* may also be of use in thalassaemia by improving blood flow and the lifespan of red blood cells, thereby reducing the need for blood transfusions, and could have crisis-averting, lifesaving benefits for people living with sickle-cell disease. So if physicians around the world were trained to prescribe appropriately prepared Cacao or dark chocolate to high-risk groups and (at higher "doses") to premorbid heart disease or diabetes patients, the cumulative reduction in morbidity, and the alleviation of human suffering which could be achieved is huge; the potential reduction to national healthcare costs, almost beyond belief.

2. Intelligent chocolate

Test subjects who ate 85g dark or milk chocolate fifteen minutes before a cognitive function test performed up to 20% better than the control group—but, interestingly, the milk chocolate group did better than the dark chocolate group in this study.[616] This could reflect the greater placebo value of familiar and comforting milk chocolate, or the anti-anxiety effects of exorphin (sedating, opiate-like) compounds in milk pairing with the compounds in chocolate (more on this topic in Chapter 7). It should be noted that fifteen minutes isn't long enough for many of the compounds in chocolate to get into the bloodstream, so all this study shows is that being given chocolate shortly before doing mental work may improve performance by undefined mechanisms.

More recent research into the chocolate eating habits of a community of 968 Americans aged twenty-three to ninety-eight over an eighteen-year period has revealed that habitual *dark* chocolate consumption is strongly linked to improved cognitive function relative to abstainers, bestowing better abstract reasoning, working memory, and visual-spatial memory among chocolate eaters.[617] As with the findings in the cardiovascular studies, these chocolate-related benefits were independent of other factors such as exercise, fruit and vegetable consumption, obesity, and general health. Another four-year study assessing the cognitive functioning of 531 older people aged sixty-five or above found that chocolate intake was associated with a reduced risk of cognitive decline—but only if caffeine intake was less than 75mg per day, suggesting that those who also drink tea or coffee or other caffeine-containing substances on a daily basis may not experience any chocolate-related brain benefits over the long term.[618]

Real-life corroboration of Cacao's possible brain benefit can be surmised from the survey of the Kuna, the group of people living in Panama who consume up to 75g of Cacao on a daily basis. In addition to lower incidence of heart attack and stroke, Cacao-drinking Kuna are noted to have much lower levels of neurological pathologies (such as Alzheimer's or Parkinson's disease) than members of the tribe who move to the city and abandon their traditional diet and lifestyle.[619] This finding will be discussed in more detail in Chapter 7, but for now I'd like to point out that the Kuna's average daily caffeine intake from Cacao is double the daily limit of 75mg caffeine in the study mentioned above, suggesting that while higher caffeine intakes from other sources may prevent Cacao from having longer-term cognition-enhancing effects, the caffeine in Cacao itself is not an issue. As we see time and again, it's inadvisable to reduce the effects of a plant to single chemical compounds when assessing real world effects: it's about the whole package.

Other lifestyle factors which differentiate between city and country living may play a role in the lower incidence of dementia and age-related movement disorders among countryside-dwelling Kuna, but the quality of their Cacao appears to be highly significant. After all, the Kuna aren't eating "sophisticated" chocolate bars, but drinking their toasted bean-based beverages. The higher polyphenol content of their traditionally-processed Cacao may be a contributing factor to their reduced risk of cognitive decline, in addition to other variables such as fewer environmental pollutants and more robust social networks in their homeland, in contrast to their relatively sickly city-dwelling relatives.

Whole Cacao bean extracts prevent Alzheimer's disease proteins from accumulating in mouse brains *in vitro*,[620] and one Cacao polyphenol (called epigallocatechin gallate, or EGCG, also found in green tea) can even halt the progression of the terminal, paralysing neurological disease amyotrophic lateral sclerosis (ALS) in mice.[621] Most interestingly, a single dose of Cacao containing 450mg flavanols, equivalent to a serving of 40g whole Cacao beans in a traditional drink, and even a third of this dose taken every day for five days significantly increased blood flow to the brain as measured by an MRI scan in human volunteers.[622] In a similar experiment, isolated flavanol mixtures from Cacao were administered to volunteers aged between sixty-one and eighty-five over an eight-week period, in a double-blind, placebo-controlled clinical trial. The outcome was that daily doses of the flavanols—equivalent to 13g and 143g of whole Cacao—dose-dependently improved performance in tests of verbal fluency and trail making (the ability to quickly link up dots: mental processing, sequencing, flexibility, and executive function), with concomitant improvements in insulin sensitivity and blood pressure at the higher dose.[623]

Another brain imaging study of blood flow in six healthy adults fed flavanol-rich chocolate showed increased signal intensity during a task requiring concentration compared to scans performed without prior chocolate consumption, although it isn't known whether this reflected increased nerve firing or just increased blood flow to the activated brain areas.[624] The assumption is that the Cacao enabled the brain to increase its blood and therefore oxygen supply as necessary—but as this was such a small trial with no placebo group that we can't be certain whether it was the chocolate or the participants' expectations which caused this response. But these findings may be of interest to people dealing with aging-related cognitive decline and dementia, especially "vascular dementia", where compromised blood flow to the brain is the root of the problem.

So we know that many compounds in Cacao have nerve and brain-cell-protecting or regeneration-promoting activity, at least in the laboratory. We know that many of these compounds get into the bloodstream after ingestion, and that some of them are capable of passing through the blood-brain barrier to reach the brain (e.g., flavanols such as epicatechin, or other polyphenols such as clovamide, resveratrol, and pyrryloquinoline quinone; the diketopiperazines; and many of Cacao's alkaloids, such as tetramethylpyrazine and trigonelline. See the *Theobroma cacao* monograph in Appendix A for detailed studies on each of these compounds and whole Cacao.) Animal experiments in rats and mice revealed that large doses of isolated Cacao polyphenols do indeed improve mental performance in tests of learning and memory, and caused acute increases in the blood level of adrenaline. To achieve such results, these experiments used rats ingesting fairly large doses of these compounds,[625] equivalent to 108–120g of whole Cacao for a human. Although the use of isolated polyphenols in animal experiments means we should be cautious in interpreting these results to infer benefit in a human population, coincidentally this dosage isn't too far from the total daily intake of Cacao for the Kuna people in Costa Rica, who have such low levels of degenerative and neurological disease.

Sleep deprivation is a commonplace cause of less pathological "neurological deficits", in other words it's known to negatively affect performance and various aspects of mental functioning such as mood and working memory. Less well known is that regular sleep deprivation increases risk of heart disease and stroke. In a recent evaluation of the effects of Cacao on working memory and circulation in thirty-two sleep-deprived volunteers, high-flavanol dark chocolate restored good circulation[viii] and working memory performance.[626] So Cacao may be the perfect remedy after pulling an all-nighter! A final interesting link between Cacao and mental functioning is the robust statistical association between higher national chocolate consumption and Nobel prizes—the more chocolate a country eats, the more likely that country is to produce Nobel prize winners.[627] Of course this association may not be causal, at least not directly—it's more feasible that chocolate-consuming countries are richer and have better education systems than non-chocolate consuming countries (generally true), or that some other factor linked to higher chocolate consumption—increased corporate sponsorship, for example—may account for this statistic. But the link is real, and worthy of further exploration.

[viii] As measured by brachial flow-mediated dilation.

While there are no high-quality clinical trials showing that chocolate can significantly impact neurological disease in humans as yet, Cacao shows promise as a nootropic drug—that is, a cognition-enhancing substance—and its circulation-enhancing properties suggest that it may be valuable for the prevention or treatment of vascular dementia and general age-related cognitive decline.

3. Asthmatic chocolate

Several substances in Cacao have anti-asthmatic activity, so in theory Cacao is a useful addition to the diet for asthmatics—which corroborates the traditional use of Cacao as a lung tonic for chronic (long-term) lung problems. A laboratory study using whole Cacao extract showed that it reduced the production of a substance called neopterin in white blood cells, indicating anti-inflammatory effects and the potential for Cacao to affect or "modulate" the immune system, perhaps damping down some types of allergic responses.[628] But this is only a lab test result, so should be taken as an "early days" finding. More potential interactions of Cacao with the immune system are discussed in Chapter 7. Similarly, the phenolic compound clovamide dilates the airways *in vitro* with the same potency as the anti-asthmatic drug Salbutamol (often marketed as Ventolin™). Clovamide was detected in the urine two hours after humans consumed Cacao beverages, indicating that it found its way into the general circulation, and might be expected to affect the lungs;[629] it has been found to allay coughing caused by inhaling chilli fumes, for example.[630] The alkaloid theophylline in Cacao even more strongly inhibits airway spasm and inflammation, as well as impairing histamine release;[631] its effects likely outweigh those of the minute amount of histamine in Cacao. Likewise, Cacao's principal alkaloid theobromine suppresses the cough reflex and slightly dilates the airways, effectively reducing persistent coughing. In children, the airway-dilating effects of both theobromine and theophylline last for two to six hours after ingestion,[632] so these effects are likely to be present in whole Cacao. Even more intriguingly, children born to mothers who consume chocolate during pregnancy have a lower incidence of asthma.[633]

4. Reproductive chocolate

A small human observational ("cohort") study found another advantage for women consuming dark chocolate during pregnancy: a significant reduction in the risk of developing high blood pressure during the pregnancy, which can cause miscarriage and other medical complications, including a serious and potentially life-threatening condition called pre-eclampsia. Higher chocolate consumption was correlated with lower blood pressure and a reduced risk of pre-eclampsia, particularly when it was regularly eaten in the first trimester, and the level of of theobromine in the umbilical cord (indicating chocolate intake before giving birth) corresponded with lower incidence of pre-eclampsia.[634]

Cacao's traditional use as a *galactagogue*—a drug to increase breast milk production, a common folk medicine use in Central America, as described in Chapter 3—hasn't yet been scientifically validated. Horsey types report success using "an old gypsy remedy", feeding cocoa powder to mares to increase their milk supply after they've foaled.[635] Administering the alkaloid salsolinol (one of the trace compounds in Cacao) to sheep increases levels of the hormone prolactin in the bloodstream, which stimulates lactation when natural endorphin levels are high.[636] So it could be that this substance is responsible for the galactagogue effect observed in folk veterinary practice, particularly as the alkaloid accumulates in the brain and has stronger effects on dopamine-releasing cells (which control the levels of prolactin) at *lower* doses. Endorphins create feelings of pleasure and comfort and raise pain thresholds when they bind to mu-opioid receptors in the brain, so when the sheep is bonding with its lamb, perhaps experiencing some discomfort from suckling, the brain releases more endorphins to increase feelings of contentment and closeness and decrease the significance of the pain. In this environment the presence of salsolinol will stimulate more milk production, reinforcing the "feedback loop" between suckling and lactation. This provides a possible mechanism by which Cacao may enhance breast milk production in mammals, as Cacao also contains other constituents which modify endorphin release, as we will see in the next chapter, where we will examine Cacao's traditional reputation as an "aphrodisiac" and its effects on male and female reproductive function.

5. Chocolate for pain control

Chocolate confectionery has been used in army rations for over a century because of its long shelf-life, high calorie density, and mildly stimulating properties. And it has proven to be useful in survival situations: the Arctic explorer Sir John Franklin praised the restorative powers of drinking chocolate, recounting how a single cup taken by a companion "seized with a shivering fit" before he slept staved off hypothermia: "The only inconvenience that he felt the next morning was pain in his limbs."[637] Part of this restorative effect, no doubt, may reside in Cacao's circulation-enhancing powers; but Cacao and chocolate also have a marked effect on pain perception.

Cacao has a long history of use for pain control. At minimum, chocolate's reputation as a palliative food or treat could reinforce a placebo response, which would diminish pain, but the flavonoids and methylxanthines in Cacao also have measurable pain-reducing effects. Caffeine alleviates several types of pain, and the flavanols suppress inflammatory responses by reducing production of inflammatory compounds and improve circulation,[638] such that consuming a flavonoid-rich dark chocolate drink after exercise diminishes next-day stiffness and pain.[639] In addition to Cacao's potential therapeutic value in syndromes which may cause or exacerbate pain, such as type 2 diabetes (as above) and obesity (see below), Cacao flavanols specifically reduce both inflammation and pain perception in *trigeminal neuralgia*, a type of facial pain which may be a result of nerve damage during dental work, for example. Cacao more generally allays pain sensitivity associated with the cranial nerves, including the vagus nerve, which has an important role in regulating digestion; these findings may partially explain Cacao's traditional use for abdominal pain.[640] But there is evidence that Cacao affects opiate signalling in the brain ("endorphins"), and Cacao is often used "unofficially" by people to self-medicate certain types of emotional pain—of which more in Chapter 5.

6. Cacao chemotherapy

Several factors increase the risk of developing cancers, including:

1. Prolonged stress, measured by raised levels of the stress hormone, cortisol, which may reduce the immune response to cancer cells[641]
2. Increased oxidative stress; for example, in smokers[642]
3. Chronic inflammation, from infections, normal aging, poor diet, or alcohol ingestion[643]
4. Carcinogenic (cancer-causing) chemicals from environmental pollutants such as lead in petrol fumes, food contaminants like fungal aflatoxins in peanuts, some medicinal drugs like cancer chemotherapy, hormone replacements like the birth control pill, industrial exposure to asbestos or toxic by-products of some manufacturing processes, etc.

Compounds in Cacao counteract or reduce the effects of all these things. Unlike the isolated polyphenols trialled in lab rats, whole Cacao acutely reduces levels of cortisol and adrenaline after ingestion by adult human males under stressful conditions;[644] it has powerful antioxidant properties, lowering levels of oxidative stress marker compounds in the bloodstream;[645] it assuages inflammation in the lining of blood vessels and elsewhere;[646] and it neutralises or blunts the effects of several carcinogens.[647] The polyphenols in Cacao prevent the transformation, growth, and spread of cancer cells in laboratory tests, although there is currently no proof that they do so in live humans.[648] But added to the diet of rats, Cacao gradually increases the general immune response to viruses and cancers,[649] and if this effect is replicated in humans it suggests that Cacao may be *chemopreventive*: a substance which reduces the risk of developing cancer. Cacao may even, to some extent, be *antineoplastic*: this literally means "against new growth"; in other words, it may stop the development of, or even kill cancer cells.

A few of Cacao's aromatic trace compounds also have anti-cancer properties, such as 2,4-nonadienal, which prevents UV light from turning cells cancerous in the laboratory. This effect is enhanced by a naturally occurring cyanide compound called benzaldehyde.[650] This is of particular interest given Cacao's combination with *mamey* seed (*Pouteria sapota*) in the traditional Cacao-based Mexican beverage known as *tejate*; *mamey* seeds, like bitter almonds, are a source of benzaldehyde compounds.[651] Theoretically, the combination of nonadienal and benzaldehyde in *tejate* in sunny Oaxaca may help protect against UV-induced cancer cell transformation. Cacao extracts also inhibit the growth of human colon cancer cells in the laboratory.[652]

Other parts of *Theobroma cacao* than the seeds are more important in traditional medicine; laboratory testing has shown that a Cacao leaf extract is toxic to one type of breast cancer cell, without affecting healthy liver cells.[653] Whether this result has any relevance to the use of Cacao leaf in traditional herbal medicine is questionable, as the solvent used was methanol, whereas most traditional preparations are made by boiling or steeping in water, or simply expressing the fresh leaf juice, and the investigation was performed in a laboratory, under highly artificial ("controlled") conditions. This kind of testing is conducted with the intent to find new drugs which can then be used to develop patentable pharmaceutical medicines, and may be of limited use to consumers of the original plant and the millions of people worldwide who rely on local herbal medicines for medical treatment. It would be far more helpful to investigate the pharmacological properties and mechanisms of action of the whole plant medicines as they are used "in the field" by the societies which have grown up with them; this would practically benefit the users of such plants, the scientific community, and the human organism at large.

So it's highly plausible that Cacao is a useful agent for reducing the probability of developing cancer. A necessary caveat is that there are many different kinds of cancer, and just because a substance is effective *in vitro*, it doesn't mean it'll be active in living human beings; nevertheless, Cacao has demonstrated a broad range of positive influences on various cancer risk factors. And as mentioned above, Cacao's theophylline content enhances the effectiveness of the chemotherapy agent, Doxorubicin: so patients undergoing Doxorubicin-based chemotherapy may benefit from incorporating Cacao into their diet, subject to their oncologist's approval (as antioxidants reduce the effectiveness of some chemotherapy drugs, so it's always important to check that any dietary changes or complementary medicines being taken are compatible with any prescription drugs).

7. The smoker's frenemy

In terms of cardiovascular disease, lung disease, and cancer risk, one group particularly stands out: smokers. Cacao and tobacco have a long, entwined history. They come from the same continent, after all. Olmec, Maya, and Mexica lords smoked tobacco and drank chocolate at banquets, and both substances had spiritual as well as earthly cachet; tobacco was a highly prized sacrament for many New World peoples, used in shamanic healing, and Cacao was a secular libation and a ceremonial drink (see Chapters 2 and 9 for more details). So perhaps it shouldn't be a surprise that their pharmaceutical interactions are interesting, too. For example, it's known that smokers metabolise (break down) caffeine 30–50% more rapidly than non-smokers,[654] because some compounds in tobacco smoke—polycyclic aromatic hydrocarbons, apparently—require the same liver enzymes to be broken down as caffeine does, so the body ups the production of these enzymes. The consequence of this is that consumers of chocolate, tea, or coffee who smoke need more of their caffeinated drug of choice to achieve the same degree of stimulation as non-smokers. Tobacco smoke also deactivates an enzyme called histone deacetylase type 2 (HDAC-2) which is important for repairing blood vessel walls, but even low doses of the alkaloid theophylline, found in Cacao and chocolate (also in tea) reactivates it, restoring its protective effects.[655]

So the banqueting Mexica, bookending their repast with smoking and chocolate, may perforce have consumed more chocolate to achieve a pleasant Cacao "buzz" than would have been necessary if they had not been smokers. And no bad thing if they did drink more chocolate, because it turns out that Cacao undoes some of the harms of tobacco. Specifically, it improves blood flow—which tobacco reduces, by constricting peripheral blood vessels—and reduces inflammation in the linings of blood vessels, which tobacco smoking aggravates.

There is another, less predictable link between Cacao and tobacco, which goes to show that few natural drug relationships are fully a one-way street. It has been noted that nicotine protects dopamine-releasing cells in an area of the brain called the *substantia nigra* from death induced by exposure to salsolinol, one of the alkaloids in Cacao.[656] Death of these neurons eventually causes the syndrome known as Parkinson's disease, in which chocolate consumption may or may not be implicated as a risk factor (see Chapter 7 for a full discussion). It's long been known that for all its damaging effects, tobacco use decreases the risk of developing Parkinson's disease. So perhaps the Mexica were right to combine tobacco smoking with ingesting Cacao at their feasts: though Cacao is by far the more beneficial of these two psychoactive drugs, and appears to accrete longevity-promoting factors as much as tobacco erodes them, it may yet transpire that each undoes a measure of the other's potential harm.

8. Campesino *antivenom*

As we have seen, Cacao is used in traditional medicine as a preventive of snakebite poisoning, a prophylactic antivenom. This seems ludicrous—what does chocolate have to offer to protect against snakebite? Nothing has been proven, but there are several possibilities. One is that the venom of many poisonous snakes increases blood clotting and inflammation in blood vessels, causing circulatory blockages, pain, and tissue death; and we know that Cacao inhibits clotting, dilates blood vessels, and reduces inflammation in blood vessel linings.

Some of the procyanidins in Cacao also inhibit an enzyme called hyaluronidase which is secreted by many pathogenic bacteria. Hyaluronidase breaks down hyaluronic acid, a component of healthy tissue, allowing bacteria to stick to and burrow into surfaces, and a lot of the compounds generated in the process also promote inflammation, increase blood vessel growth, and modify immune system functions.[657] The hyaluronidase inhibitory activity of Cacao goes some way towards explaining its traditional use as a general or supportive tonic in many illnesses including cancer and lung ailments, and possibly its use as a prophylactic "antivenom" against some types of snakebite—because many snake venoms, too, contain hyaluronidases, and inhibiting this enzyme with plant extracts significantly reduces their morbidity (ability to cause suffering, harm, and death) in experimental animals.[658] But Cacao hasn't yet been tested here, so this is currently an intriguing speculation; it's very doubtful that Cacao ingestion could neutralise snake venom, but it's credible that prior ingestion of Cacao could attenuate the effects of some kinds of snake venom, perhaps even making the difference between life and death.

9. Chocolate for beauty and longevity

Cacao causes blood vessels to dilate, so it should facilitate circulation to the skin, just as it does to other organs such as the brain, heart, liver, and kidneys. And so it does: two hours after ingesting Cacao, blood flow to the skin increases by 70%.[659] This is another reason why Cacao is good for smokers—smoking reduces the blood supply to the skin, and Cacao can restore it! I have an anecdotal example of this effect. Two or three times a week, I drink a half pint of a basic chocolate *atole* (my *champurrado* recipe—see Chapter 8) for breakfast or lunch. In September 2016 I had a small growth on my left arm biopsied: a small chunk was cut out to investigate in a lab. When I returned home two or three hours later, I had my usual *champurrado*-style *atole* for lunch. An hour or so later I was watching a film when I felt warm liquid running down my arm. The wound was bleeding to the extent that the dressing was absolutely soaked and the blood had seeped through it: it looked like a bullet wound. After twenty minutes holding my arm above my head while using my left hand to find and apply the styptic powder in my first aid kit and a suitable dressing, I made a note to myself: do not take strong chocolate immediately after any surgical procedure!

This increase in dermal blood flow has an advantage with more popular appeal: slowing down skin aging. A twelve-week double-blind study testing the effects of high-flavanol cocoa in a group of twenty-four women found that those women ingesting the equivalent of 30–40g whole Cacao per day had a significant reduction in signs of sun (UV light) damage such as reddening of the skin, with measurable improvements in skin texture and hydration, although, sadly, no changes in wrinkles were noted.[660] Another thirty-person double-blind trial confirmed that high flavanol cocoa (presumably equivalent to ordinary, good quality Cacao) increased the skin's resistance to sun damage over a twelve week period.[661]

Apart from the possibility of better skin and a sharper mind as you get older, ingesting Cacao may help you live longer. A retrospective review of a group of 470 men aged 65–84 from the "Zutphen Elderly dietary and lifestyle study" conducted in the Netherlands between 1985 and 1990 found a reduced risk of *all-cause mortality* associated with the *highest* levels of cocoa and chocolate intake. After controlling for BMI, smoking, lifestyle, drugs, diet, and caloric intake, cocoa enthusiasts had a 47% reduction in relative risk of death from *all causes put together* during the study period, as compared with non-chocolate consumers.[662] Consuming chocolate only one to three times a month has been correlated with a whole extra year of life in population studies.[663]

High stress levels, associated with elevated blood cortisol, are known to be associated with a shorter lifespan. With excessive stress we literally age faster. The chromosomes in every cell in our body—the bundles of genetic information in the nucleus of each cell—are protected by buffers or caps at each end, called telomeres. Every time a cell replicates itself, these telomeres get worn away, just a little, and an enzyme called telomerase helps to repair them. One study compared the telomeres of women with healthy children to those who had children with chronic health issues, and found that the more stressed women (mostly those with chronically sick children, this being a cause of ongoing worry and stress) were more likely to have shorter telomeres, much less telomerase, and even looked older.[664] As mentioned above, and as we shall see in the next chapter, Cacao may help to lower blood levels of adrenaline and the stress hormone, cortisol.[665] Although Cacao's effect on telomeres and telomerase hasn't been assessed, its notable effect on stress hormone and its traditional reputation would suggest a positive influence.

Paradoxically, Cacao may also have anti-obesity effects, related to the presence of polyphenols. Laboratory research showed that cocoa powder reduced fat production in fat cells, and inhibited digestive enzymes which help break down starch and fats in the digestive tract prior to absorption.[666] In animal studies, rats fed cocoa as part of their diet had less weight gain, and obese diabetic rats fed a high-fat diet for thirteen weeks had less weight gain when Cacao polyphenols were added to the diet. The polyphenols appear to reduce the expression of genes which allow fatty acids (the building blocks of fat) to be manufactured in the liver; they do the same for some cholesterol-making genes, and increase the production of genes which accelerate fat-burning. These effects seem to hold true in human populations: a random selection of just over a thousand healthy people of between twenty and eighty-five years old showed that regular chocolate eaters had a lower BMI, even though their overall calorie consumption was higher.[667] It's possible that these results may be explained if the chocolate consumers were richer (of "higher socio-economic status") overall, which is positively associated with lower levels of obesity and health problems in general, perhaps due to comparatively lower stress, leading to lower cortisol levels—high cortisol encourages weight gain, producing an "apple shaped" body with abdominal fat accumulation. But, of course, we know that Cacao reduces cortisol levels—so either way, Cacao may help!

Traditionally, though, Cacao was used to "fatten", or gain weight. This isn't necessarily a contradiction: the high fat content and nutritional benefit of adding Cacao to the diet of an underweight person would help them gain weight, while the stress-modulating and metabolism-modifying effects may have a different effect in an overweight population. It's very likely that any "weight-reducing" properties may be nullified by the addition of excess sugar and a high-fat, high-meat diet, if the burgeoning incidence of obesity in contemporary Mexico is anything to go by. All else being equal, it seems that Cacao may contribute to keeping us alive for longer, maintaining a healthy body weight, and even helping us to endure the ravages of time a little better too.

* * *

So ingesting real, traditionally prepared Cacao-based beverages—or even good quality dark chocolate with a high cocoa content—may help to prevent and even treat many of the most significant health challenges of the affluent world. Cardiovascular disease, diabetes, some types of cancer, and many age-related problems such as cognitive decline, chronic pain, or respiratory conditions—even, to some extent, the aging process itself—can potentially be ameliorated by the judicious use of Cacao, albeit preferably in combination with significant lifestyle and dietary adjustments. While Cacao may turn out to be almost as beneficial as our ancestors thought, and far more useful than we believed for the prevention and treatment of many ailments, we should also remember that life is complex, and there's no such thing as a panacea. Even a substance as beneficial and pleasant as Cacao isn't a universal solution. Natural drugs are complex, and the friendliest pharmaceuticals or most flavoursome foods offend some bodies, a subject to which we shall return in Chapter 7. But in the next chapter we'll delve a little deeper into Cacao's reputation as a psychotropic drug and an aphrodisiac, and attempt to tease out the subtle truth of its effects on mood and perception.

Señora Anna Maria Garcia Vásquez winnowing Cacao, Juchitan, Guatemala, 2018

Half-ground Cacao seeds on a metate.