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Mood Components in Cocoa and Chocolate: The Mood Pyramid

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ABSTRACT

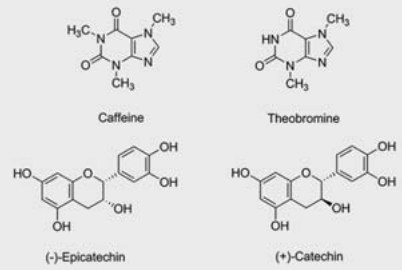
Cocoa and chocolate, prepared from cocoa beans that originate from the fruits of the cocoa tree *Theobroma cacao*, have a long-standing reputation as healthy food, including mood-enhancing effects. In spite of many clinical trials with chocolate, cocoa, or its constituents, the mechanisms of action on mood and cognition remain unclear. More in particular, it is still controversial which constituents may contribute to the psychopharmacological activities, ranging from the major cacao flavanols and methylxanthines to the minor amines, amides, and alkaloids. In this review a critical appraisal is made of recent studies on mood and cognition, with a special emphasis on analytical characterization of the test samples. It is concluded that the mood and cognition-enhancing effects of cocoa and chocolate can be ranked from more general activities associated with flavanols and methylxanthines, to more specific activities related to minor constituents such as salsolinol, with on top the orosensory properties of chocolate. Therefore, the "mood pyramid" of cocoa and chocolate is proposed as a new concept. To understand the role and interactions of the different major and minor constituents of cocoa, it is recommended that all test samples used in future *in vitro*, *in vivo*, or human studies should be phytochemically characterized in much more detail than is common practice today.

ABBREVIATIONS

BDI	Beck Depression Inventory
CES-D	Center for Epidemiologic Studies – Depression Scale
CF	cocoa flavanols
CNS	central nervous system
CoCoA	cocoa, cognition, and aging
DSST	digit symbol substitution test
fMRI	functional magnetic resonance imaging
GABA	gamma-amino-butyric acid
HVA	homovanillic acid

Introduction

Chocolate is produced from cocoa beans, originating from the fruits (cocoa pods) of *Theobroma cacao* L. (Malvaceae), the cocoa tree. Processed raw seeds are known as cocoa. Processing involves fermentation, drying, roasting, winnowing, alkalization, and conching [1–4]. Cocoa and its derived products contain a wide range of phytochemicals. The main constituents from a quantitative point of view are methylxanthines and flavan-3-ols (including proanthocyanidins) [5]. Methylxanthines occur in tea (*Camellia sinensis* [L.] Kuntze, Theaceae), coffee (*Coffea* sp., Rubiaceae), and cocoa. The most widespread methylxanthine is caffeine (1,3,7-trimethylxanthine) (▶ **Fig. 1**); in addition to tea and coffee, it is found in many plant species that are used in various parts of the world to prepare drinks with a stimulating effect on the CNS, such as *Paullinia cupana* Kunth (guarana) (Sapindaceae), *Ilex paraguariensis* A. St.-Hil. (maté) (Aquifoliaceae), and *Cola* sp. (kola nuts) (Malvaceae). The distribution of theobromine (3,7-dimethylxanthine), on the other hand, is much more restricted, *T. cacao* being



▶ **Fig. 1** Major constituents of *T. cacao*.

the major natural source. In spite of its structural similarity to caffeine, theobromine is much less active on the CNS [6–9]. The polyphenolic fraction includes monomeric compounds such as (−)-epicatechin and (+)-catechin (▶ **Fig. 1**), proanthocyanidins such as dimeric (B-type) and trimeric (C-type) procyanidins, as well as higher oligomers. Minor constituents include flavonols and anthocyanins, stilbenoids, phenolic acid derivatives, and various amides and amines [5]. Fermentation and processing may lead to important changes in phytochemical composition from fresh beans to chocolate [3]. Naturally occurring polyphenolics are lost, while Maillard reaction products are formed. Therefore, the polyphenolic content of commercial chocolate products depends not only on the raw material, but also on processing factors [10, 11]. The dietary consumption of cocoa and dark chocolate, rich in polyphenols, has been associated with many beneficial effects on human health, especially on the cardiovascular system [12]. Much attention has also been paid to chocolate as "food for moods" [13]. Chocolate has a reputation as a unique psychoactive food, taking sometimes almost mythical proportions, as already exemplified by the name of the genus *Theobroma*, which means in fact "the food of the gods" [14]. The aim of this review is to have a critical look at actual original research papers, especially the more recent studies. A literature search was carried out in the SciFinder and PubMed databases, using the search terms "cocoa" and "mood" or "cognition." In addition, studies cited in these papers or in previous reviews were selected to address the question whether or not there is evidence for any "mood effects" of cocoa and/or chocolate and, if so, to discuss the class or classes of phytochemicals that may contribute to these effects. Therefore, all studies involved will be scrutinized from a phytochemical point of view. Indeed, in view of the high degree of variation in composition that can be expected for commercial cocoa and chocolate products, related to differences in genotype, geographical origin, fermentation, and further processing, it is amazing to see how little attention is paid in many studies to proper characterization of test samples. This creates a high degree of uncertainty about which components might be responsible for positive results and if negative results may be due to poor quality and low levels of biologically active ingredients of the test materials or cocoa/chocolate products used.

Human Studies on Mood Effects and Cognitive Function of Cocoa, Chocolate, and Their Constituents

In a recent review dating from 2017 on tea, cocoa, coffee, and affective disorders, Garcia-Blanco et al. [15] identified six human studies related to cocoa consumption and depression, anxiety, or affective disorders published between 2007 and 2016. In four of these studies, cocoa intake and affective disorders were positively associated [16–19]. Only the cocoa extract used in the study by Ibero-Baraibar et al. [16] was fully analytically characterized: participants were given 1.4 g of cocoa extract per day, containing 140 mg theobromine, and 645 mg total polyphenols, specified as 414 mg flavanols expressed as catechin, 153 mg epicatechin, 15 mg catechin, 99 mg procyanidin B2, 13 mg procyanidin B1, and 134 mg oligomeric procyanidins. The effects of cocoa extract supplementation for 4 wk were studied in a double-blind, randomized, placebo-controlled parallel nutritional intervention in a population of overweight or obese middle-aged subjects as part of an energy-restricted diet. Depressive symptoms were evaluated by means of a questionnaire (BDI) and were found to be reduced in both the cocoa group and in the control group, which might be due to weight loss. Anxiety symptoms were not affected. In both groups, plasma HVA (3-methoxy-4-hydroxyphenylacetic acid) levels were increased, which is known to be positively correlated with central dopaminergic activity; brain dopamine is related to mood. However, in the cocoa group, HVA levels were significantly higher than in the placebo group. Although the authors claim that plasma HVA is a more objective parameter for a psychological status than a subjective questionnaire such as the BDI, at the same time they mention that there still is a lot of controversy with regard to the interpretation of plasma HVA concentrations [16]. In addition, it should be pointed out that HVA also is a metabolite formed from catechin and epicatechin by microbial conversions in the colon and subsequent liver metabolism [20], which may also account at least in part for the difference between both groups. Martin et al. [17] observed that eating a milk chocolate snack, but not dark chocolate (both without analytical characterization), resulted in a decrease of anxiety; the latter finding was in agreement with the previous study. In the study by Pase et al. [19], participants received 20 g of a chocolate drink containing 500, 250, or 0 mg (placebo) polyphenolic compounds; all treatments contained 240 mg theobromine and 40 mg caffeine. After 30 d of treatment, self-rated calmness and contentedness, but not cognitive performance, were improved for the highest dose of polyphenols. Apparently, the methylxanthines are not involved in this effect. Apart from these positive studies, two negative ones were reported by Garcia-Blanco et al. [15]. Balboa-Castillo et al. [21] assessed chocolate consumption in a cohort of 4599 individuals based on a validated computerized diet history, and no association was observed between physical or mental aspects of quality of life related to health and chocolate intake. Cross-sectional analysis of a sample of 1018 adults showed that higher CES-D scores were associated with higher chocolate consumption [22]. Apparently, chocolate consumption is higher in a depressed population, but it remained unclear if there was a causal connection

and, if yes, in which direction. Garcia-Blanco et al. [15] concluded that drinking tea, cocoa, or coffee could protect against depression but that, however, most of the evidence came from observational studies. From the six studies discussed in this review, only one allowed to relate the effects observed to a particular class of constituents (i.e., the polyphenols rather than the methylxanthines).

In 2013, Scholey and Owen [23] published a review in which they investigated if chocolate or its individual (groups of) constituents were capable of influencing mood or cognitive function. "Cognition" is not easy to define, as it involves attention, perception, memory, language, executive, and psychomotor functions; in addition, these factors can be influenced by others such as the arousal and energetic level and "mood" [24]. A total of 21 randomized clinical trials with appropriate outcomes were found, 14 with regard to mood and 12 with regard to cognition (some studies addressed both aspects, although a distinction is not always easy to make); a series of studies was excluded for various reasons, leaving 6 and 7 papers, respectively, that were included in their review. Studies were ranked by means of a modified augmented Jadad scale based on 10 methodological factors, one of which being "Was the amount administered documented," which does not necessarily imply detailed analytical characterization.

With regard to the studies on mood effects, Scholey et al. [25] compared three cocoa drinks containing a low (46 mg), medium (520 mg), or high (994 mg) level of total CF but similar levels of caffeine (46.4, 43.5, and 40.6 mg, respectively) and theobromine (400.2, 429.2, and 458.2 mg, respectively). Both the medium and high dose of CF acutely reduced mental fatigue and improved performance during demanding cognitive processes in healthy, young participants (although this may be considered an effect on "cognition" rather than on "mood"). The medium dose appeared to be more beneficial. Therefore, these effects were attributed to the CF fraction rather than to the methylxanthines, and it was hypothesized that this might be related to well-established effects of CF on endothelial functionality and blood flow (see below). Some other "mood" studies reviewed by Scholey and Owen [23] examined whole chocolate without analytical characterization. Therefore, it was not possible to draw any conclusion about the contribution of different constituents or classes of compounds to the observed effects. Macht et al. [26, 27] reported elevated mood or reduction of negative mood. Weisenberg et al. [28] observed an amelioration of increased anxiety due to the experience of an unsolvable task, but there was no statistically significant difference between different treatments, including treatments not involving chocolate, cocoa, or its constituents. Mitchell et al. [29] investigated if theobromine and caffeine had synergistic effects (in a 5 : 1 ratio as in chocolate) on cognition, mood, and blood pressure in a randomized double-blind, placebo-controlled crossover trial. The study included four measurement days, on which participants received placebo, 750 mg theobromine, 120 mg caffeine, or the combined dose of both methylxanthines. As expected, caffeine increased alertness and blood pressure, in contrast to theobromine, which had no effect on alertness but decreased blood pressure, thus confirming that theobromine lacks the CNS-stimulating properties of caffeine. No treatment effects on psychomotor performance using the DSST were observed. Also the study by Smit et al. [7] focused on the role of the methylxanthines: in a first study a dark chocolate bar containing theobromine (250 mg) and caffeine (19 mg) was tested against a placebo (microcrystalline cellulose); in a second study visually identical chocolate-like portions containing no methylxanthines, low doses (100 and 8 mg, respectively) or high doses (250 and 20 mg, respectively) were evaluated, corresponding to white, milk, and dark chocolate. A 25-item mood questionnaire was used. Four factors (constructs) were defined, and the cocoa powder as well as the theobromine/caffeine combination were able to increase "energetic arousal" and "hedonic tone." Because the profiles of effects observed for cocoa powder and its methylxanthine constituents were almost identical, the authors concluded that the latter ones were responsible for the mood and cognitive effects.

With regard to the studies on cognitive and neurocognitive functions reviewed by Scholey and Owen [23], three of these have been discussed above [7, 25, 29]. In addition, Francis et al. compared a high-flavanol (172 mg CF) and a low-flavanol (13 mg CF) cocoa drink administered to young female subjects. Based on fMRI, they reported that the flavanol-rich cocoa drink increased blood flow to relevant areas of the brain [30]. However, no effects on behavioral responses were evident. There was no information on the concentrations of other constituents in the cocoa drinks. Crews et al. [31] were not able to support beneficial effects on some neuropsychological and cardiovascular parameters on a short-term of consumption of a dark chocolate bar or a cocoa beverage. Also in this case, only information on the level of polyphenolic compounds was provided. Camfield et al. [32] found no behavioral effects of daily consumption of a chocolate drink with a medium (about 250 mg) or high (about 500 mg) concentration of flavanols compared to a low (about 0 mg) flavanol treatment (placebo) during 30 d in middle-aged (40–65 y) volunteers. Again, there was no information on other constituents. However, Field et al. [33] found that dark chocolate consumption (with 773 mg CF, 222 mg theobromine, and 38 mg caffeine) was able to acutely improve cognitive and visual functions as compared to white chocolate, which contained only a low amount of CF, theobromine, and caffeine. Although the authors concluded that these effects may be explained by increased cerebral blood flow induced by CF, it should be noted that the control treatment with white chocolate was not only low in CF, but also low in theobromine and caffeine.

Some other studies are available that had not been included in the two review papers cited above. In the CoCoA study, Desideri et al. [34] evaluated cocoa drinks with high (about 990 mg), intermediate (about 520 mg), and low (about 45 mg) levels of CF containing similar amounts of macronutrients, minerals, theobromine (458, 429, and 400 mg, respectively), and caffeine (41, 44, and 46 mg, respectively). Participants were elderly people with mild cognitive impairment. After 8 wk of treatment, their cognitive functions were improved. In the second part of this study, it was tested if regular consumption of the same cocoa drinks improved cognitive performance in elderly people with normal cognitive functions [35]. Indeed, it was found that regular consumption of CF can improve some aspects of cognitive dysfunction related to age. The same observation was made by Brickmann et al. [36] in a controlled randomized trial of healthy elderly people con-

suming a high (900 mg CF per day) or a low (10 mg CF per day) CF-containing diet for 3 mo; theobromine and caffeine doses were similar in both treatments (172 mg vs. 156 mg and 16 mg vs. 14 mg, respectively). This observation was related to enhanced dentate gyrus function in the brain, established by fMRI. Also, Lamport et al. [37] studied the effect on healthy older adults of a cocoa drink rich in flavanols (494 mg) compared to one poor in flavanols (29 mg) but containing similar levels of other constituents such as theobromine (185 mg vs. 176 mg) and caffeine (15 mg vs. 17 mg) on cerebral perfusion using fMRI in an acute, placebo-controlled, crossover clinical trial. It was concluded that consumption of CF improved regional cerebral diffusion, and it was hypothesized that this may be associated with a beneficial effect on cognitive performance. Massee et al. [4] reported that administration of a cocoa tablet with a known amount of catechin polyphenols (250 mg) and caffeine (5.56 mg) was able to acutely improve some aspects of cognitive performance and attenuate mental fatigue in young, healthy adults compared to placebo treatment. Also, caffeine, not only the polyphenols, may be involved in this effect. Grassi et al. [38] compared flavanol-rich dark chocolate (520 mg/bar) with flavanol-poor chocolate (88.5 mg/bar). It was evaluated if the effects of sleep deprivation could be counteracted in healthy individuals, and a positive influence of CF on vascular impairment and working memory performance was observed. However, the flavanol-poor chocolate also contained much less theobromine and caffeine (419 mg vs. 1200 mg and 48.98 mg vs. 108.8 mg, respectively). Crichton et al. [39] carried out a longitudinal study with 968 participants, the dietary intake of which was assessed using a questionnaire. It was concluded that habitual chocolate intake may exert beneficial effects on cognitive performance and may slow down the age-related decline of cognitive functions.

Cocoa Flavanols, Methylxanthines, Cognitive Functions, and Mood

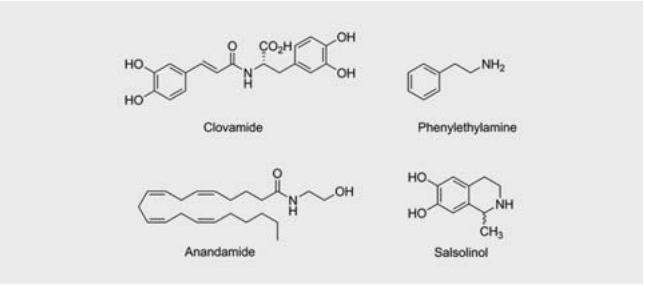
Taken altogether, based on the studies discussed above, many good reasons appear to state that cocoa and its constituents have cognitive and mood-related effects. However, many different experimental setups are used to measure cognitive function and mood, and a lot of studies lack detailed analytical information on the test samples. Although mixed and sometimes seemingly contradictory results have been obtained, apparently CF as well as the methylxanthines are involved. Studies pointing toward CF as the cognitive-enhancing constituents of cocoa are in line with the enormous amount of scientific evidence supporting the health effects of phenolic compounds in fruits and beverages, particularly their protective effects against chronic diseases, including cardiovascular and neurodegenerative diseases [40]. Consumption of flavonoid-rich plant foods is known to improve cognitive performance, and a range of molecular mechanisms underlying these effects has been established [41–44]. Flavonoids or their metabolites interact with particular signaling pathways in the brain, and they have beneficial vascular effects, especially with regard to cerebrovascular blood flow. They reduce neurodegenerative processes and neuroinflammation and stimulate neurogenesis in the hippocampus. In addition, cardiovascular health is closely related to cognitive performance [45]. Epicatechin, the most abundant flavanol in cocoa, displays various beneficial effects on the CNS by stimulating perfusion, angiogenesis, and neurogenesis. It induces changes in neuron morphology, especially in regions involved in memory and learning [24]. Whereas monomeric flavanols can be absorbed in the small intestine, procyanidins will be metabolized in the colon by the intestinal microflora to phenolic acids that may be absorbed [12, 46, 47]. It should be noted that also these small phenolic compounds can contribute to mood effects. For example, anxiolytic activity has been demonstrated *in vivo* for phenylacetic acid derivatives such as *p*-hydroxyphenylacetic acid and 3,4-dihydroxyphenylacetic acid [48]. Although cocoa is particularly rich in flavanol derivatives, a subclass of the large group of flavonoids, compared to many other food sources, their effects on cognition seem to be a general feature of the flavonoids rather than a specific effect of CF. Even if the cognition-enhancing activity of cocoa is mainly due to the flavanol fraction, it seems unlikely in view of the unique position and reputation of cocoa and chocolate that only CF are responsible for mood-related and cognitive effects.

This is where the second class of major constituents of cocoa (i.e., the methylxanthines theobromine, and caffeine) comes in. Some studies discussed above indeed pointed toward the methylxanthines as psychoactive constituents, and in addition it should be noted that in some cases the observed effects have been attributed to the flavanol fraction, although analytical information on other constituents such as the methylxanthines was lacking. The methylxanthines can easily cross biological membranes and distribute through body fluids. Whereas the psycho-stimulatory action of caffeine is well established, the situation of theobromine is less clear. Methylxanthines are known as adenosine-receptor blocking agents; caffeine (blocking the A1 and A2A subtypes) is more potent than theobromine [8, 9, 49]. In a randomized, double-blind, placebo-controlled trial by Baggott et al. [50], young, healthy adults received theobromine (250, 500, or 1000 mg), caffeine (200 mg) or placebo. Whereas caffeine showed psychopharmacological and cardiovascular effects as expected, theobromine had only limited subjective effects at a dose of 250 mg and negative mood effects at higher doses. Judelson et al. [51] compared different cocoa drinks containing low, medium, or high amounts of CF, caffeine, and theobromine with control drinks containing no CF, caffeine, or theobromine; only caffeine (100 mg dose); or mainly theobromine (400 mg dose) and a small amount of caffeine. It was concluded that theobromine at nutritionally relevant doses does not influence mood or vigilance. Therefore, it seems that the combination of theobromine and caffeine is involved in the unique psychopharmacological properties of cocoa and chocolate, rather than the individual substances. This was also evident from some studies discussed above. At least they occur in cocoa and chocolate in amounts that may lead to pharmacologically relevant concentrations in the body and the brain when consumed in a realistic quantity, in contrast to some of the minor constituents discussed below.

Psychopharmacological Activities of Minor Constituents

Finally, the question can be raised if some of the minor constituents occurring in cocoa and chocolate might be involved in the psychopharmacological effects. Clovamide (*N*-caffeoyl-3-*O*-hydroxytyrosine) (▶ **Fig. 2**) is a typical example of the class of the *N*-phenylpropenoyl-L-amino acids, which are known to contribute to the astringent taste of cocoa beans and nibs [52]. Their content strongly decreases during the roasting process [53]. There are no studies or indications that this class of compounds contributes to the psychoactive effects of cocoa or chocolate. Rather, clovamide shows a good structural similarity with rosmarinic acid, a well-known anti-inflammatory phenolic compound, and indeed it exhibits similar properties (inhibition of respiratory burst, of pro-inflammatory cytokine release, and of NF-κB activation).

Other psychoactive constituents may include biogenic amines such as tyramine, tryptamine, and especially phenylethylamine (▶ **Fig. 2**), which has been referred to as a "love drug." Nevertheless, it is only present in low concentration, and it does not reach the brain after oral intake [54, 55]. Anandamide (▶ **Fig. 2**) and related *N*-acylethanolamines such as *N*-oleoylethanolamine and *N*-linoleoylethanolamine are endocannabinoids, suggesting they may play a role in the psychopharmacological properties of cocoa and chocolate. However, anandamide is only present in small concentrations and, in addition, is unstable. In contrast, it seems that the potential role of the tetrahydroquinoline alkaloids such as salsolinol has largely been neglected or overlooked. Indeed, the hypothesis by Melzig et al. [56] that the dopaminergic activity of salsolinol might play an important role in the mood effects of cocoa or chocolate has not been investigated in more detail. This paper has hardly been cited in most reviews on the mood and cognition effects of cocoa or chocolate. Salsolinol can be present as a racemate in cocoa and chocolate up to a concentration of 20–25 µg/g. It is an alkaloid derived from dopamine, and it was found to bind to the dopamine D_3-receptor, especially (*S*)-salsolinol. The D_3-receptor is known to play a role in the reward system. Based on the observed K_i value of about 0.5 µM, it was hypothesized that the amount of salsolinol typically ingested by consuming about 100 g of dark chocolate was sufficient to reach a pharmacologically relevant concentration. In addition, salsolinol has an indirect dopaminergic effect, at least in rats, by activating μ-opioid receptors on GABAergic neurons [57, 58]. Both the *R*- and *S*-enantiomer of salsolinol were found to act as agonists of the μ-opioid receptor, the *S*-isomer being the more potent one [59]. However, it has been reported that salsolinol only has a poor ability to pass the blood-brain barrier [60]. Nevertheless, it has been observed that the bioavailability of active constituents in complex matrices like plant extracts is improved by co-effectors that influence their solubility and/or transport, as it was observed for hypericin [61]. This may also apply to salsolinol and other constituents of *T. cacao*. In the same way as the tetrahydroisoquinoline alkaloids are related to dopamine, the tetrahydro-β-carboline alkaloids are related to tryptamine. Also the latter class of alkaloids has been detected in cocoa and chocolate, but in rather low concentrations, and it remains questionable if they play a role in the psychopharmacological properties [58, 62].



▶ **Fig. 2** Some minor constituents of *T. cacao*.

▶ **Fig. 3** The mood pyramid: from general effects related to the flavanols, over more specific effects of methylxanthines and minor alkaloids, to the unique orosensory properties of chocolate.

Conclusion

The relationship between cocoa or chocolate and mood is highly complex, and the specific mechanisms by which behavior, cognition, and mood are modulated are still not fully understood. Different classes of compounds are involved, and synergistic relationships may play a role, but this has hardly been explored yet. Whereas this review essentially focused on phytochemical constituents and their pharmacological properties, it has been established that also the orosensory properties of chocolate can at least in part explain the desire to ingest chocolate and can contribute to mood effects [13, 23, 55]; this may even be true to a lesser extent for, for instance, cocoa drinks, but obviously this does not apply to cocoa preparations or individual compounds administered as capsules. Therefore, we would like to propose the "mood pyramid" as a model, summarizing the more general up to the more specific psychopharmacological actions of cocoa and chocolate (▶ **Fig. 3**). There is a large amount of scientific evidence that the flavonoids, more in particular CF, are involved in the cognition-enhancing effects, although this may not be very specific for cocoa or chocolate, since these constituents are widely distributed in nature and in food. At the second level, the methylxanthines caffeine and theobromine have additive and maybe synergistic ef-

fects on cognition and alertness, although the role of theobromine remains unclear. Methylxanthines are less common in nature than flavanols, but still not restricted to *T. cacao*. At the third and gradually more specific level, the tetrahydro-isoquinoline alkaloids, more in particular salsolinol, may exert additive or synergistic activities. Finally, at the fourth level, the orosensory properties of cocoa drinks and certainly chocolate are the icing on the cake. By its unique combination of sweetness, taste, and texture, chocolate is one of the most palatable foods, contributing to mood effects.

To understand the role and interactions of the different major and minor constituents of cocoa, a first prerequisite is that all test samples used in *in vitro, in vivo,* or human studies should be phytochemically characterized in much more detail than is common practice today. In many cases, only the amount of cocoa flavonols is mentioned, and in fewer cases the levels of caffeine and theobromine. Concentrations of minor constituents are hardly reported, although at least for salsolinol it is clear that its contribution to the effects on mood and cognition deserves to be investigated in more detail. Depending on geographical origin and processing, the phytochemical composition of cocoa and chocolate can be highly variable. Only by comparing different test samples with different analytical profiles can the role of the various constituents of cocoa and chocolate be unraveled and potential synergistic effects be rationalized.

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Conflict of Interest

The authors declare they have no conflicts of interest.

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