Antidepressant-like properties of cocoa’s polyphenols

The role of flavanoids and flavanols on depression

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ABSTRACT: In the last ten years, cocoa and bitter chocolate with a high content of cocoa have received much attention due to their significant polyphenol contents, and thus, have been recognized as significant sources of phytochemicals with healthful effects. Increasing evidence from experimental preclinical and clinical studies using cocoa polyphenolic extracts or dark chocolate suggest an important role for these high-flavanol-containing products in various human pathologies. In fact, cocoa’s polyphenols are susceptible to induce stimulant, relaxant, euphoriant, tonic and antidepressant effects. This article reviews the various cocoa’s flavonoids, aiming to establish their implications on mood state, particularly on depression, a major public health problem affecting about 12 percent of the world population.

KEYWORDS: cocoa composition, polyphenols, flavanols, depression, oxidative stress, neuroinflammation.

INTRODUCTION

Cocoa (Theobroma cacao) and bitter chocolate with a cocoa content of 70 percent or higher are widely known for their effects on mood state, particularly depression related symptoms (1). These products contain a complex mixture of essential nutrients like carbohydrates, lipids, proteins, vitamins, minerals, and several biologically active compounds, including caffeine, theobromine, tryptophan, phenylethylamine and cannabinoid-like fatty acids. Besides these constituents, polyphenols are a quantitatively important group in cocoa and may also represent promising beneficial therapeutic agents, in particular in cardiovascular diseases, cancer, diabetes and neurodegenerative pathologies (2). This review presents some generalities regarding cocoa and its antidepressant-like effects, and outlines more specifically the potential biofunctional activity of flavanols.

COCOA COMPOSITION

Carbohydrates, phenylethylamine, methylxanthines, anandamides and magnesium

Among active compounds present in cocoa, carbohydrates are probably closely related to well-being described after eating chocolate. Important data have been mentioned by Parker and collaborators (1) relating to carbohydrates: their abilities to promote a feel-good sensation during atypical depression and the possibility to identify the phenomenon of craving as a form of self medication in different types of depression, particularly in chocolate. Phenylethylamine is chemically and pharmacologically related to catecholamines and amphetamine and the deficit in this endogenous compound may contribute to depression state (3).

The most important methylxanthines found in cocoa and chocolate are caffeine and theobromine. Like carbohydrates, caffeine could be a self-medication for people who suffered from depressive symptoms. For example, sedation is an important symptom in depression and methylxanthines can induce a benefit arousal through an interaction with adenosine receptors (4). Cocoa and chocolate contain several unsaturated N-acyltyethanolamines, which are structurally related to anandamide (5). High levels of these latter substances could interact with other active compounds of chocolate and provoked a well-being sensation.

Finally, magnesium, one of the most quantitatively important mineral in cocoa, is potentially effective to treat depression in relation with the intraneuronal magnesium deficits in depressive patients (6).

Polyphenols and flavanols

The antidepressant properties of polyphenols could be closely related to their antioxidant effects. Oxidative stress caused numerous damages during several psychopatologies (7). Depression is associated with elevated antioxidative enzyme activities and lipid peroxidation, and interestingly, the most common antidepressant agents, like selective serotonin re-uptake inhibitors (SSRIs) and tricyclic antidepressants (TCAs), are able to counteract these deleterious effects [8-10]. In this way, it must be noted the high antioxidant properties of flavanols of cocoa. Lee and collaborators had compared the phenolic and flavonoid contents and total antioxidant capacities of red wine, tea and cocoa (11), and then concluded: (i) that cocoa contained much higher levels of total phenolics and flavonoids (expressed in epicatechin equivalents) per serving than black or green tea and red wine and (ii) that cocoa exhibits the higher antioxidant activity (cocoa > red wine > green tea > black tea).

Flavanols, also chemically defined by flavan-3-ols, are an important subclass of polyphenols, included in flavonoids. Typical flavanols consist in catechin, epicatechin, epigallocatechin and epigallocatechin gallate. Cocoa contains only (+)-catechin and (−)-epicatechin, while tea contains mainly (−)-epicatechin gallate and (−)-epigallocatechin gallate (12). The procyanidins are the oligomeric counterparts of the flavanols and are constituted exclusively of the monomers epicatechin and catechin.
The polyphenol content of raw cocoa beans differs from that of cocoa powder or chocolate. Raw cocoa beans are rich in flavanol monomers and epicatechin-based procyanidin oligomers from dimers to decamers. Finally, chocolate type also influences the content of flavanols, such as dark chocolate contains more than three times as much catechin as milk chocolate (13).

**ANTIDEPRESSANT-LIKE EFFECTS OF COCOA**

Many flavonoids have been reported to exert antidepressant-like activity in different animal models. For example, among the compounds evaluated in the forced swimming test (FST) we can note: flavonoids contained in Hypericum perforatum (14, 15), hyssop and isouserchitin presents in Apocynum venetum (16), quercetin (17), the aqueous extract of Cecropia glaziouli Sneth, rich in catechins, procyanidins and others flavonoids (18) or rutin isolated from the ethanolic extract from Schinus molle (19). Alternative methods of evaluation, like chronic mild stress, had showed similar results with others flavonoids: liquiritin had showed similar results with others flavonoids: liquiritin extracted from Glycyrrhiza uralensis (20) or icariin, isolated from Epimedium brevicornum (21).

In a recent work, we have demonstrated that a cocoa polyphenolic extract, containing high levels of flavonoids, exhibits an antidepressant-like effect in the FST paradigm in rats (22). In this study we were not able to determine the specificity of polyphenols involved in the antidepressants-like effect of cocoa; however, the results pave the way to a reflection on the impact of flavanols in the regulation of oxidative stress.

**Ability of flavonoids to cross the blood-brain barrier**

Today, the biological actions of flavanols, like flavonoids, appear more related to the modulation of intracellular signalling cascades and gene expression or the interactions with mitochondria, rather than a simply influence on the intracellular redox status (23). So an important preliminary question is the ability of flavanols to interact with the central nervous system (CNS). Youdim et al. (24) had studied interaction between flavonoids and the blood-brain barrier and had demonstrated that a higher lipophilicity of compounds is associated with a better penetration. So the more polar flavonoid, such as epicatechin and their glucuronidated metabolites may not be able to access the brain. However, the study of Abd El Mohsen and collaborators (25) had previously demonstrated the presence of epicatechin glucuronide and its 3′-O-methylated epicatechin glucuronide in the brain tissue. Similar results had been observed with miquelianin, a quercetin found in Hypericum perforatum (26).

**Pathogenesis of depression, oxidative stress and neuroinflammation**

The existence of an immunological activation during depression is well-established (27) and the activation of immune cells is associated with overproduction of reactive oxygen species (ROS). Moreover, on the one hand, there is a relation between ROS production and lipid peroxidation (28), and abnormalities in lipids and depression, on the other hand (29).

Today, the interest of compounds like flavanols for the treatment of depression is reinforced by numerous reports concerning antioxidant status of antidepressants. Zafir et al. (30) have recently demonstrated that a chronic administration of different antidepressant agents in rats (fluoxetine, imipramine and venlafaxine) induced: (i) a decline in the activity of several enzymes, such as superoxide dismutase and catalase; (ii) a normalization of lipid peroxidation. In addition, Bilici et al. have presented results in human indicating that several SSRIs were able to regulate antioxidative enzyme activities and lipid peroxidation (8).

Besides oxidative stress, prolonged exposure to inflammatory cytokines in the brain may underlay a heightened neuroinflammatory response that may lead to impairments such as depression (31). Interestingly, Li et al. had shown that catechin and epigallocatechin gallate attenuate microglia and/or astrocyte-mediated neuroinflammation, notably via an inhibition of cytokine release (32).

Taking together all these complementary data strongly suggest that flavanols, through their high antioxidant activities, could regulate oxidative stress, such as the well-characterized pharmacological antidepressant drugs. Their role in the CNS could be more complex in relation, specially, with the modulation of intracellular signalling cascades, gene expression, interactions with mitochondria or neuroinflammation.

**CONCLUSION**

Polyphenols and flavonoids in general, and flavanols in particular, appear today as a new and interesting opportunities to regulate mood disorders. Thus, cocoa flavanols could be a useful possibility that permit to have the benefit of chocolate as therapy, without an excessive and potentially adverse effects linked to carbohydrates and lipids.

Today, the main development of flavonoids and flavanols is turned to neurodegenerative disorders, like Alzheimer or Parkinson syndromes (23). This situation corresponds to the great interest developed around activities of flavonoids to assure a protection against neuronal injury induced in neurodegenerative diseases (33). However, there is a growing body of evidence to suggest that flavonoids and flavanols may be able to play a role in the prevention and/or the treatment of mood disorders by (i) the demonstration of their high antioxidant capacities, and the ability of pharmacological antidepressant agents, i.e. SSRIs and TCAs, to exert neuroprotective effects on the CNS oxidative damage, (ii) their effects on the more complex phenomenon of neuroinflammation, which could be predominant in the chronic development of depression. Further studies are necessary to identify the active constituents with antidepressant-like activity among the various cocoa’s polyphenols and to understand their mechanism of action in the brain.
REFERENCES AND NOTES