REVIEW ARTICLE

Health Benefits of Bioactive Compounds from Cocoa (*Theobroma cacao*)

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Abstract

Cocoa is regarded as a super food due to its high nutrient content and proven health benefits. Cocoa beans are rich in carbohydrate (31%), protein (11%), fat (54%), fiber (16%) and minerals. Cocoa is a good source of bioactive compounds too. The major bioactive components are polyphenols constituted of flavonoids and non-flavonoids. The bioactive components with rich antioxidants and anti-inflammatory activities contribute to various health benefits. The flavonoid-rich chocolates improve peripheral vascular function. The consumption of cocoa or chocolate is beneficial in inhibiting the complex molecular process leading to cancer. Flavonoids in cocoa increase insulin sensitivity by improving endothelial function and reducing oxidative stress. The cocoa flavonoids also penetrate and accumulate in the brain regions involved in learning and memory. The knowledge of bioactive compounds in cocoa and cocoa products suggests that they could be consumed as a part of wholesome, health-promoting nutritional food.

Keywords: Bioactive compounds, Cocoa, Flavonoids, Health benefits, Non-flavonoids, Polyphenols.

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Introduction

Nature has a huge, effective, and wonderful collection of plant species that offer several beneficial properties to human nutrition and health. These plant species represent important sources of raw materials essential for maintaining human existence and improving his quality of life. The cocoa tree, which forms the basis for one of the world's most popular food products chocolate, has a rich history involving many cultures and carrying important economic and social implications to millions of peoples worldwide. The health-promoting properties of cocoa have also been celebrated by the ancient Mesoamerican society with historical records revealing more than 150 applications of cocoa for medicinal purposes. In recognition of its multiple health benefits, the Mayans gave cocoa its ancient name "Kakawa" which translates into "Food of the Gods." The scientific name of cocoa is *Theobroma cacao* in which, "theo" means "God" and "broma" means "food". It can be used as a curative drug and culinary delight.

Cocoa and cocoa-derived products comprise one of the most popular, and it contains a high density of essential nutrients like carbohydrate, protein, fat, polyphenol and minerals. These major nutrients come under the category of primary metabolites. Secondary metabolites are molecules that are not essential for growth and development, but they are biosynthetically derived from primary metabolites, e.g., alkaloids, glycosides, phenolics, terpenoids. These secondary metabolites are called bioactive compounds. Biologically active compounds/phytochemicals present in biological systems defined as non-nutritive plant chemicals that have protective or disease preventive properties (Bernhoft, 2010).

The high polyphenolic content of cocoa, coupled with its widespread presence in many food items, renders this food of particular interest from nutritional and pharmacological viewpoints. Cocoa contains approximately 380 known chemicals and 10 psychoactive compounds. Due to the high content of monomeric (epicatechin and catechin) and oligomeric (procyanidin) flavanols, as well as methylxanthines (theobromine and caffeine), cocoa and chocolate may be considered as functional foods. Therefore the bioactive compounds in cocoa have proven health benefits, aids in improving the elasticity of blood vessels, help to reduce high-fat diet induced obesity, helps to maintain the healthy circulatory system, beneficial for maintaining a healthy brain and helps to reduce LDL cholesterol and glucose level.

The cocoa, as part of the wonderful nature, provides mankind a wide variety of valuable food products and health benefits. There are several proven health benefits by the intake of cocoa and cocoa-based products for the cardiovascular system, cancer, neurological/nervous system, endocrine system, diabetes, dermatological system, and stress.

Coco and Cardiovascular System

Cardiovascular disease is the leading cause of death. Numerous studies have suggested beneficial effects of cocoa

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in cardiovascular diseases (CVD). The cardioprotective effects of cocoa are due to the following factors:

- Flavanols inhibit platelet activation and aggregation
- Decrease LDL cholesterol and increase HDL cholesterol
- Maintaining blood pressure
- Reduces endothelial dysfunction

Flavanols Inhibit Platelet Activation and Aggregation

Platelet Activation

The basic function of platelets rapidly binding to damaged blood vessels, aggregate to form thrombi and to prevent excess bleeding. When platelets are circulating through vessels with an intact, healthy endothelium, the platelets remain in their original, inactivated state. The absence of activating factors and the release of prostacyclin (prostaglandin I2) by the healthy endothelium supports this state.

However, when a platelet encounters a break in the endothelium, it encounters molecules that trigger its activation. One such molecule is collagen, which is characteristically found almost everywhere except inside a blood vessel.

When platelets are activated, it will cause thrombus formation, aggregate at the site of atherosclerotic plaque and prevents blood flow. The atherosclerotic plaques are formed in the artery wall by the accumulation of fats and reduce the blood flow and cause atherosclerosis.

The antiplatelet effect of flavonoids in cocoa is due to the inhibition of thrombus formation by enhancing the production of vasodilating factor nitric oxide (NO).

Role of Cocoa in Endothelium-dependent Vasodilation and Inhibition of Aggregation of Platelets

Figure 1 indicates that flavanol-rich cocoa due to its chemical structure improves the vasodilatation of the artery by producing nitric oxide. Theobromine inhibits platelet aggregation in the blood vessels. Nitric oxide has an inflammatory effect and counteracting platelet aggregation at the site of inflammation.

Murphy *et al*. (2003) conducted a study on platelet count and platelet aggregation after cocoa flavanol supplementation. For the study, sixteen active and placebo group was selected. The study was conducted for 28 days.

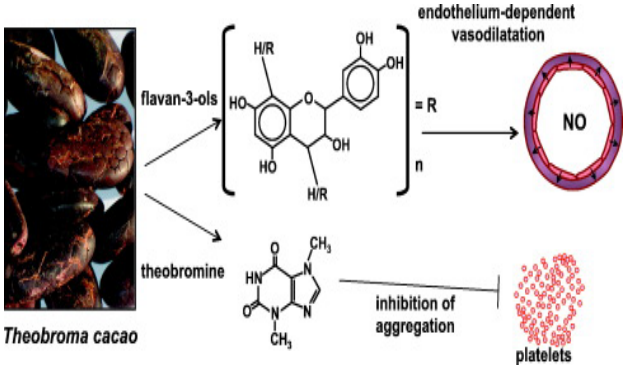


Fig. 1: Flavanol-rich cocoa increase vasodilation and inhibit platelet aggregation

Table 1: Platelet count and platelet aggregation after cocoa flavone supplementation

Mean platelet count (× 109/L)	*Active group (n = 16)*		*Placebo group (n =16)*	
	Day 0	Day 28	Day 0	Day 28
	253.1 ± 61.2	244.4 ± 51.5	208.9 ± 37.6	218.5 ± 35.1
Aggregation (ω/s)	0.07 ± 0.04	0.06 ± 0.04	0.05 ± 0.03	0.07 ± 0.03

Cocoa flavanol drink was given for the active group and placebo group without cocoa flavanol drink. It is clear from Table 1 that the group those who consume cocoa flavanol drink have less platelet count and aggregation compared to the placebo group.

Bioactive Compounds in Cocoa Decrease LDL Cholesterol and Increase HDL Cholesterol

There are two main types of cholesterol: high-density lipoprotein (HDL) and low-density lipoprotein (LDL). Lipoproteins are made of fat and proteins. HDL is known as "good cholesterol" because it transports cholesterol to the liver to be expelled from the body. LDL is called “bad cholesterol” because it takes cholesterol to arteries, where it may collect in artery walls. Too much cholesterol in arteries may lead to a build-up of plaque known as atherosclerosis. This can increase the risk of blood clots in arteries. If a blood clot breaks away and blocks an artery in the heart or brain, may have a stroke or heart attack.

Modification of low-density lipoprotein (LDL) appears to play a vital role in atherosclerosis. A number of endogenous factors have been oxidizing LDL cholesterol. Myeloperoxidase (MPO) is an enzyme to participate in the metabolism of nitrogen dioxide (NO); it will cause peroxidation of LDL cholesterol. Nitrite, its oxidation product, serves as a substrate of MPO-forming reactive nitrogen species.

The function flavonoids in cocoa will scavenge the free radicles (reactive nitrogen species) nitrogen dioxide and reduce lipid peroxidation of LDL.

Baba *et al*. (2007) conducted a study on the effect of supplementing cocoa powder on LDL and HDL cholesterol levels. Normal diets are given for two groups, and an extra 26 grams of cocoa was given to the cocoa group for twelve weeks. After the study, they observed that LDL cholesterol of control group was decreased from 135.90 to 131.72. But in the cocoa group, there was a drastic decrease in LDL cholesterol from 135.13–118.14. In the case of HDL cholesterol in the cocoa group, it was increased from 52.50 to 55.21 and in the cocoa group, it was increased from 52.89 to 65.25. They concluded that after twelve weeks LDL cholesterol was decreased and HDL cholesterol was increased in cocoa group cocoa compared to control group (Table 2).

Bioactive Compounds in Cocoa reduce Blood Pressure

Blood pressure is the force that blood exerts against the wall of a blood vessel. Under pathological conditions, reactive oxygen species are produced in the artery wall, this will cause

Table 2: Effect of supplementing cocoa powder on LDL and HDL cholesterol levels

Duration	*LDL cholesterol (mg/dL)*		*HDL cholesterol (mg/L)*	
	Control group	Cocoa group	Control group	Cocoa group
Baseline	135.90	135.13	52.50	52.89
Week 12	131.72	118.14	55.21	65.25

Table 3: Reduction in systolic and diastolic blood pressure based on cocoa intake

Cocoa intake	*Lowest*	*Middle*	*Highest*
Blood pressure (mm Hg)	(0.36 g/d)	(0.36–2.30 g/d)	(2.30 g/d)
Systolic	149.6	148.8	147.0
Diastolic	84.5	83.7	82.2

hyper tension. The function polyphenol in cocoa increased nitric oxide bioavailability and improve arterial stiffness and endothelial function.

Buijsse *et al.* (2006) supplemented cocoa powder in three different concentrations like lowest (0.36 g/d), middle (0.36–2.39 g/d) and highest (2.30 g/d) to three different groups of BP patients for three weeks (Table 3). After the study, they observed that the group those who consume the highest level of cocoa (2.30 g/d) have 147.0 g/d systolic and 82.2 g/d diastolic blood pressure. But the other two groups (middle and lowest cocoa intake) have the systolic blood pressure 148.8 g/d and 149.6 g/d and diastolic blood pressure 83.7 and 84.5, respectively. They concluded that the group those who consume the highest level of cocoa have less systolic and diastolic blood pressure compared to middle and lowest cocoa intake groups.

Downstream Effects of Cocoa Polyphenols in the Cardiovascular System

The downstream effects of cocoa polyphenols in the cardiovascular system with nitric oxide as the target group is represented in Figure 2. Endothelium dysfunction, lipoprotein oxidation, platelet aggregation, and inflammation will cause cardiovascular risks. Endothelium nitric oxide synthase will reduce all these cardiovascular risks.

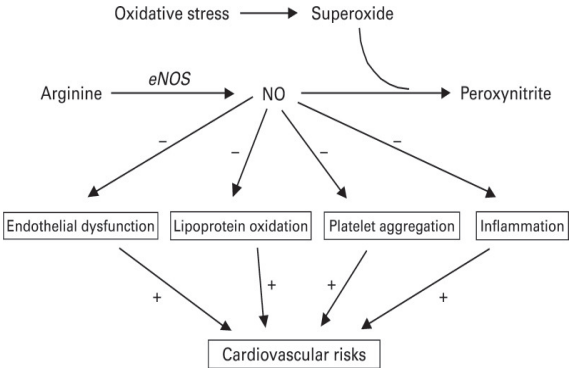


Fig. 2: Downstream effects of cocoa polyphenols in the cardiovascular system

Cocoa and Cancer

Cancer is a disorder which is characterized by abnormal growth of cells. This abnormal growth and multiplication caused by free radicals.

The anticarcinogenic property of cocoa is due to the following factors mentioned below:

Prevents Oxidation of Free Radicals

Cocoa contains a high antioxidant activity. Free radicals damage the components of a cell including the DNA and lead to the development of cancer. Antioxidants combine with and prevent free radicals from causing any harm to the body (Fig. 4).

John, (2001) indicates that cocoa and dark chocolate contain more polyphenol having more antioxidant index compared to the other two products like milk and white chocolates. It is evident from the table that cocoa and dark chocolate contain the polyphenol content of 224 and 126 µmol/g and its antioxidant index were 710 x 10^3 and 500 x 10^3, respectively. Compared to cocoa and dark chocolate, milk and white chocolate contain less polyphenol (52.2 and 8.2 µmol/g) and antioxidant index. In white chocolate, the antioxidant index was nil (Table 4).

Polyphenols Control the Abnormal Cell Growth

Bioactive compounds in cocoa help to control the abnormal cell growth by interacting with the mechanism of a cell. It does so by changing the structure of the cell membrane of these abnormal cells. It is responsible for interacting with

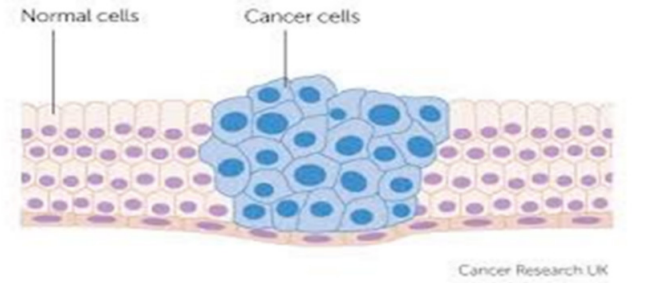


Fig. 3: Uncontrolled multiplication of normal cells to cancer cells

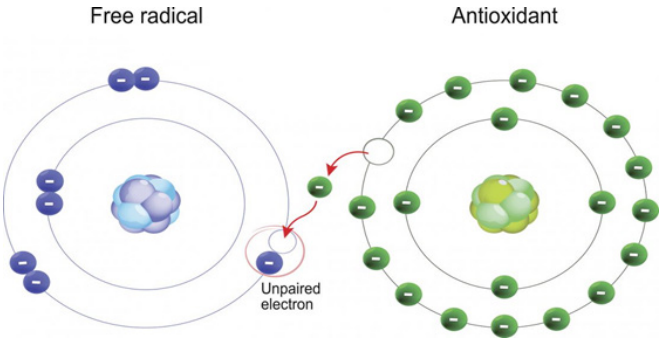


Fig. 4: Antioxidants prevents the oxidation of free radicals

Table 4: Antioxidant properties of cocoa and chocolate polyphenols

Products	*Polyphenols (µmol/g)*	*Antioxidant index x 10^3*
Cocoa	224 ± 66.4	710 ± 21.3
Dark chocolate	126 ± 17.4	500 ± 20.4
Milk chocolate	52.2 ± 20.4	136 ± 36.3
White chocolate	8.2 ± 2.9	-

Table 5: Cancer preventive effects of cocoa polyphenols in animal models

Polyphenols	*Concentration*	*System studied*	*Effects*
Procyanidin	50–57.9 µg/mL	Abdomen	↓Cell growth
Epicatechin	14.5–29 µg/mL	Colon	↓TNF induced oxidant formation
Catechin	34.8 µg/mL	Colon	↓TNF induced oxidant formation

the production of enzymes responsible for inducing tumor growth and malignancy. Another effect of polyphenols is on the nucleic acid, including DNA.

Martin *et al*., 2013 conducted a study on cancer preventive effects of cocoa polyphenols in animal models. Polyphenol like procyanidin, epicatechin, and catechin was supplemented to animals at different concentrations for abdomen and colon cancer. Procyanidin was given at the concentration of 50–57.9 µg/ml for animal suffering from abdominal cancer, epicatechin was given at the concentration of 14.5–29 µg/mL for colon cancer and catechin was supplemented in a quantity of 34.8 µg/mL for animals with colon cancer. At the end of the study, they found that there is a decrease in cell growth and TNF induced oxidant formation in cancer suffering animals. TNF is a tumor necrosis factor is responsible for initiating the growth of cancer cell and spreading those cells into various body parts. After the study, they concluded that bioactive compounds in cocoa have beneficial effects for reducing cancer (Table 5).

Beneficial Effects of Cocoa for Diabetes

Diabetes mellitus (DM) is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. In normal healthy person beta cells of the pancreas produce the hormone insulin and maintain the glucose level in our body. Diabetes is due to either the pancreas not producing enough insulin or the cells of the body not responding properly to the insulin produced. There are two main types of diabetes mellitus. Type 1 DM results from the pancreas's failure to produce enough insulin, referred to as "insulin-

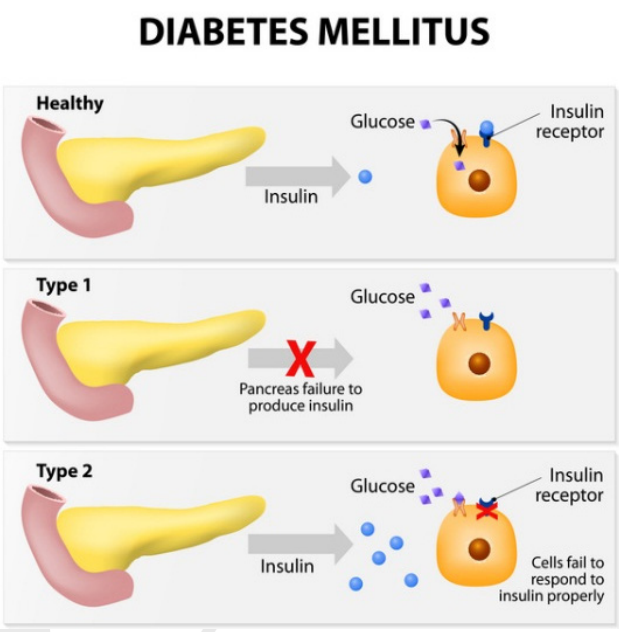


Fig. 5: Types of diabetes

Table 6: Effect of cocoa powder on the fasting blood glucose level of the experimental rats

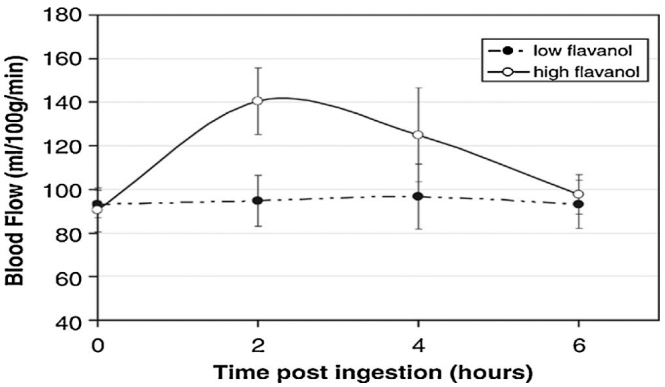
Groups	*Initial fasting blood glucose (mg/dL)*	*Final fasting blood glucose (mg/dL)*
Normal (control)	79.5	82 .0
Diabetic (control)	378 .0	367 .0
Diabetic + 2% cocoa powder	418 .0	144 .0

dependent diabetes mellitus" (IDDM) or "juvenile diabetes". Type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly (Fig. 5). As the disease progresses a lack of insulin may also develop. This form was previously referred to as "non-insulin-dependent diabetes mellitus" (NIDDM) or "adult-onset diabetes". The function of the bioactive compound in cocoa, especially epicatechin will increase insulin production and control blood sugar levels and help beta cells work better and become stronger.

Olasope *et al*. (2017) conducted a study on the effect of cocoa powder on the fasting blood glucose level of the experimental rats. For this study, they selected three groups of rats, fist normal control, second diabetic control and third one diabetic and also giving 2% cocoa powder. Initial fasting blood glucose level and final fasting blood glucose level of three groups tested. From Table 6, it is clear that the third group those who consume 2% cocoa powder have a drastic decrease in final fasting blood glucose level from 418.0–144.0 mg/dL.

Effect of Cocoa on Nervous System

Cocoa flavanols were attributed to enhance blood flow, promote brain perfusion, and protect from neuro



Graph 1: Blood flow response to cocoa flavanol drink

degradation and neuronal injury. For optimal brain functioning, cerebral blood flow (CBF) needs to be well maintained to support constant oxygen and glucose supply to neurons as well as waste excretion. Increase in CBF represents a potential means to improve cerebral function. The principal polyphenols that enhance CBF in humans come mainly from cocoa.

Sokolov *et al*., (2013) conducted a study on patients those having less blood flow response, by giving low flavanol and high flavanol cocoa drink to two groups. At the end of the study, they found that the group those drinking high flavanol drink have increased blood flow up to140 ml/100g/min compared to low flavanol drinking group. In the low flavanol drinking group, there was no change in blood flow from initial and also after post ingestion of low flavanol drink (Graph 1).

Cocoa Polyphenols Promote Brain Perfusion

Brain perfusion is the amount of blood taken up by certain areas of the brain. Cocoa flavanol intake will increase perfusion in Anterior Cingulate Cortex (ACC) and parietal cortex. According to Patel *et al*., (2008) blood perfusion in ACC and parietal cortex increase attention, learning capacity and taste monitoring ability.

Protection from Neurodegradation and Neuroinflammation

Flavonoids in cocoa exert a multiplicity of neuroprotective actions, including the capacity to protect neurons from damage induced by neurotoxins, reduce neuroinflammation, and promote memory, learning, and cognitive function. These effects are related to two common processes, flavonoids interact with signalization cascades involving protein and lipid kinases that lead to the inhibition of neuronal death by apoptosis induced by neurotoxicants (such as oxygen radicals) and to the promotion of neuronal survival and synaptic plasticity. Concurrently, they induce beneficial effects on the vascular system and on CBF mainly by improving endothelial function and stimulating angiogenesis. Via these mechanisms, the lifelong consumption of flavonoid-rich nutrients has the potential ability to limit neurodegeneration and prevent or even reverse age-related cognitive decline. Flavanols in cocoa increase cerebral blood flow and induce angiogenesis and new cell growth in the hippocampus. Angiogenesis is the formation of new blood vessels from existing blood vessels.

Several studies have looked at the relation between antioxidant intake and dementia, most often the risk of Alzheimer's disease. In Alzheimer's disease, excessive production and deposition of amyloid beta (Aβ) peptide lead to microglial activation, and the resultant production of inflammatory mediators further boosts Aβ production and induces death and dysfunction of neurons. The main symptom of Alzheimer's disease is the loss of memory. So the cocoa flavanol will increase angiogenesis and new cell growth in the hippocampus and thereby reduce the symptom of Alzheimer's disease.

Cocoa and Skin Health

Skin is prone to the development of several diseases, and the mechanisms in the pathogenesis of aged skin are still poorly understood. However, a growing body of evidence from clinical and bench research has begun to provide scientific validation for the use of cocoa-derived phytochemicals as an effective approach for skin protection. The bioactive compounds of cocoa may have a positive impact on skin health. When we are exposed to ultraviolet light, it will cause overproduction of reactive oxygen species (ROS). This will cause activate inflammation, accelerate physiologically, and epidermal degeneration. The antioxidants in cocoa scavenge these free radicles and reduce the skin problem and increase skin health.

Heinrich *et al*., 2006 conducted a study on the evaluation of skin structure and texture consuming high flavanol (329 mg/d) and low flavanol (27mg/d) cocoa beverages. For the study, they selected 24 females between the age group of 20 to 65 years. They gave flavanol drink for twelve weeks. After twelve weeks of study, they observed that roughness of skin was decreased from 0.27 to 0.19 at the end of the 12th week in high flavanol drinking group. Scaling and wrinkles also decreased from 0.14 to 0.8 and wrinkles from 42.2 to 41.8. But the smoothness was improved in the high flavanol cocoa group from 20.3–21.2. Finally, they concluded that the groups who consume high flavanol drink have less roughness, scaling and wrinkles, and improved smoothness compared to low flavanol groups (Table 7).

Cocoa and Antistress Effect

Stress is defined as "the non-specific response of the body to any demand for change." The effects of stress on public health are profound. Stress may be caused due to physical, psychological and environmental factors.

Mechanism of Stress

During stress, the hormone cortisol is released. Cortisol is mainly released through hypothalamus pituitary adrenal (HPA) axis, which involves the hypothalamus, pituitary gland, and adrenal gland. Hypothalamus release corticotropin-

Table 7: Evaluation of skin structure and texture consuming high flavanol and low flavanol cocoa beverages

Parameters	*Concentration of flavanol*	
	High flavanol	*Low flavanol*
	(329 mg)	*(27 mg)*
Roughness		
0 W	0.27	0.13
6 W	0.20	0.17
12 W	0.19	0.15
Scaling		
0 W	0.14	0.18
6 W	0.10	0.11
12 W	0.08	0.13
Smoothness		
0 W	20.3	19.6
6 W	20.9	20.7
12 W	21.2	20.5
Wrinkles		
0 W	42.2	44.4
6 W	41.8	44.0
12 W	41.8	43.7

W, Weeks

releasing hormone (CRH), which stimulate the anterior pituitary produce adrenocorticotropic hormone (ACTH) which stimulate the adrenal cortex to produce cortisol. The action of flavanol in cocoa was to modulate and inhibit the hyper secretion of stress releasing hormone ACTH and cortisol. Hypothalamus pituitary adrenal (HPA) axis function and inhibits the hypersecretion of ACTH and cortisol (Fig. 6).

Sunny and Latiff (2007) conducted a study on the effect of cocoa flavanol in reducing stress. For the study, they selected sixty samples and divided them into three groups (i) dark chocolate (DC), (ii) milk chocolate (MC), (iii) white chocolate (WC). Each group contains twenty members. Subjects answered a perceived stress scale (PSS)-10 questionnaire at baseline and after consumption of chocolate (40 g/day) for 2 weeks. After two weeks they observed that the groups those consuming dark chocolate have the higher post-intervention value of 55 ± 3.62, while other two groups of white and milk chocolates less post-intervention value (15.5 ± 6.09 and 14.70 ± 5.75) (Table 8). It was less than the baseline value of perceived stress scores were analyzed and Means were compared across the study groups by one-way analysis of variance (ANOVA) and within the same group by paired 't' test. After the study, they concluded that the consumption of 40 g dark chocolate daily for 2 weeks appears to be an effective way to reduce perceived stress.

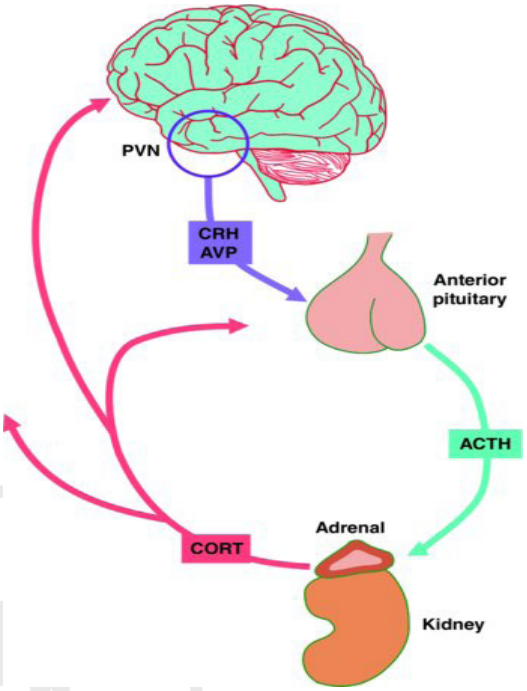


Fig. 6: Sress and HPA axis

Table 8: Effect of flavanols in reducing stress

Groups	*Perceived stress scores (Mean ± SD)*	
	Baseline	*Post-intervention*
Dark chocolates	17.95 ± 4.50	55 ± 3.62
Milk chocolates	17.65 ± 5.93	15.5 ± 6.09
White chocolates	16.35 ± 5.52	14.70 ± 5.75

Conclusion

Cocoa is rich in bioactive compounds. The knowledge of bioactive compounds in cocoa and cocoa products suggests that they can be considered as a part of wholesome, health-promoting nutritional food. Provides a wide variety of valuable food products and have potential health benefits. Knowledge of its various medicinal properties represents a stimulus to those involved with its production, processing, and consumption. Recently, science has advanced significantly in improving our understanding of the various features of chocolate that contribute to its popularity, and its after-effects of consumption on human health have also been extensively studied. Although it's marketing as a health product is not a priority, eating in moderation, mainly the darker forms could potentially have many beneficial results. But one thing is certain, both from a scientific viewpoint as sensory, chocolate is enjoyed as a favorite food for most of the people. The immense scope in developing neutraceuticals from cocoa has yet to be explored. Neutraceuticals are the substances, foods, or parts of food that provide medical and pharmaceutical health benefits.

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