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DARK CHOCOLATE- A TEMPTING DRUG

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ABSTRACT

Dark chocolate is a very complex food and scientists continue to investigate it in order to unlock its potential benefits and secrets. Cocoa and cocoa derivatives have recently attracted the attention of many investigators and general public because of their potential nutritional, medicinal and mystical properties. Studies have shown that dietary supplementation with flavonoid rich cocoa and dark chocolate may exert a protective and preventive effect on human health. Dark chocolate consumption plays an important role in reducing the risk of chronic conditions including the cardiovascular diseases, central nervous system, diabetes and immune system related diseases. Some of the identified benefits of flavonoid rich dark chocolate include its antioxidant properties, improved endothelial function, decrease in blood pressure and modulation of the immune system. Dark chocolate has also been reported to have aphrodisiac and mood lifting effects. New studies have claimed that dark chocolate could improve the brain function and help keep Dementia and Alzheimer at bay. Cocoa polyphenols in dark chocolate also show anticariogenic activity and thus prevent tooth decay. Maintaining the overall health has become crucial in today's world. This review article mentions all the beneficial effects of cocoa polyphenols in dark chocolate thus stating that dark chocolate is not just a mere delicacy, but also an effective tempting drug.

KEY WORDS: Flavonoids, dark chocolate, antioxidant property, human health.

INTRODUCTION

In general chocolate is considered to be a dense suspension of solid particles, with an average solid concentration of about 60 to 70% from cocoa, sugar and milk (depending on the type) properly dispersed in a continuous fat phase, which consists mostly of cocoa butter.[1] The

main chocolate categories are dark, milk and white, differing in their content of cocoa solid, milk fat and cocoa butter. The outcome is varying proportions of carbohydrate, fat and protein content.[2] Dark chocolate is also known as 'bittersweet' or 'semisweet' chocolate. It contains a high percentage (≥ 60%) of cocoa solids, and little or no added sugar. Dark chocolate has a rich, intense flavour, and is found in chocolate bars, candies and baking chocolate.

It is found that 40-g serving of milk chocolate provides 394 mg of cocoa flavonoids, whereas dark chocolate contains 892 mg. A hot cocoa mix, in contrast, contains 45 mg of cocoa flavonoids in a 240-mL serving.[2,3]

Judging from reported research on cocoa and chocolate, milk chocolate has been less of an object of investigation than dark (black) chocolate. The reason for this is that the amounts of polyphenols in milk chocolate are smaller than in dark chocolate due to the lower amount of cocoa liquor used in milk chocolate (about 10±15%) compared with that of dark chocolate (about 30±50%). Dark chocolate thus seems to have higher potential as being the most beneficial to human health.[1,2]

Source of Dark Chocolate: "Cocoa" is derived from cacao, which is taken from the Mayan and Aztec languages. Dark chocolate is derived from cocoa beans, *i.e.* the fruits of the tree *Theobroma cacao*. Theobroma (Greek word for "food of the Gods") is from the family of *Sterculiaceae*.[1,2,4] There are mainly two principal types: Criollo, constituting about 5% of the world's cocoa production, and the more common Forastero, which has smaller, flatter, purple beans. A third variety, Trinitario (a more disease-resistant hybrid of Criollo and Forastero), is regarded as a flavour bean.

Contents in Dark Chocolate: Polyphenols in cocoa beans are stored in the pigment cells of the cotyledons. Depending on the amount of anthocyanins those pigment cells, also called polyphenol-storage cells, range in color from white to deep purple.[1,4]

Three groups of polyphenols can be distinguished as Catechins or flavan-3-ols, Anthocyanins and Proanthocyanidins. The main catechin is epicatechin with up to 35% of polyphenol content. Phenolic compounds make up 12–18% of the total weight of dried cocoa nibs (i.e., roasted cocoa beans). Approximately 35% of the total content of polyphenols in non-fermented cocoa nibs belonging to the Forastero variety is epicatechin. Epicatechin content in

fermented cocoa nibs of different varieties range between 34.65 and 43.27 mg/g (defatted sample), this amount decreases during the process of fermentation and drying.[2,5]

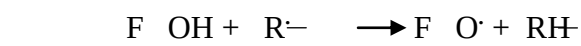
Apart from flavan-3-ols, catechin, epicatechin and their dimers procyanidin B1 and procyanidin B2, which are major compounds in cocoa, the following polyphenols have been identified and quantified in cocoa beans or cocoa products: procyanidin B3, procyanidin B4, procyanidin B5, procyanidin C1, procyanidin D, higher oligopolymers, mostly homologues of epicatechin with 2-18 monomeric units, as well the following flavanols: quercetin, quercetin-3-O-glucoside (isoquercitin), quercetin-3-O-galactoside (hyperoside), quercetin-3-O-arabinoside. Moreover following flavones have been detected: apigenin, apigenin-8-C-glucoside (vitexin), apigenin-6-C-glucoside (isovitexin), luteolin and luteolin-7-O-glucoside, dihydroquercetin, dihydroxykaempferol, kaempferol rutinoside, naringenin, naringenin-glucoside, myricetin-glucoside. The following phenolic compounds are identified: phenylethylamine, caffeic acid, chlorogenic acid, coumaric acid, ferulic acid, phenylacetic acid, phloretic acid, protocatechuic acid, syringic acid, vanillic acid, clovamide and dideoxyclovamide.[1,3]

PROBABLE MECHANISM OF ACTION

i. As anti-oxidants

Human body cells are threatened by oxidative damage every now and then. The reactive oxygen species generated by various mechanism in the system cause cellular damage. [6] This damage is caused due to shift in net charge of the cells and change in osmotic pressure, thus leading to swelling and death of the cell. It is stated that an average healthy cell undergoes free radical attack approximately 10,000 times every hour. This is why we need an endless supply of antioxidants.[3,7]

- **Direct radical scavenging activity:**



Phenolic groups of flavonoids serve as a rich source of a readily available ‘H’ atoms. They have the ability to donate these ‘H’ atoms. This hydrogen donating ability is attributed to the antioxidant effect.[3,8,9]

- **Modulation in Nitric Oxide (NO) activity**

Nitric oxide derived from constitutive *NO synthase* in small quantity is beneficial but if in large concentration (activity derived by induced *NO synthase* in macrophages) lead to cell

damage.[10] The induced NO react with free radicals and form peroxynitrite radical which cause lipid the free radicals, thus inhibiting their reaction with NO leading to lesser damage.[6,10,11]

- ***Xanthine oxidase* inhibition**

Xanthine oxidase is one of the most the important enzyme in the system which helps in the conversion of xanthine to uric acid. In reperfusion phase during chronic diseases, *xanthine oxidase* which serves as a source of oxygen free radical reacts with molecular oxygen and form superoxide free radicals which lead to oxidative injury. Flavonoids in dark chocolate inhibit these enzymes thereby resulting in decreased oxidative damage.[8,12]

ii. Action on leukocyte immobilisation

During ischemic conditions, there is a lot of formation of oxygen derived free radicals. In such conditions, leukocytes get immobilised and adhere firmly to the endothelial wall and stimulate degranulation of the neutrophil. As a result of this, oxidants and other inflammatory mediators are released resulting in injury to the tissues. It was found that oral administration of a purified micronized flavonoid fraction was reported to decrease the number of immobilized leukocytes during reperfusion. Flavonoids in dark chocolate decrease the number of immobilised leukocytes and help in inflammation like conditions. Some flavonoids can inhibit degranulation of neutrophils without affecting superoxide production. The inhibitory effect of some flavonoids on mast cell degranulation was shown to be due to modulation of the receptor-directed Ca^{2+} channels in the plasma membrane.[3]

iii. Interaction with enzyme system

Flavonoids act by reducing the release of peroxidase. This helps to inhibit the production of reactive oxygen species by neutrophils. Another interesting fact is flavonoids inhibit the metabolism of arachidonic acid. Arachidonic acid is said to be the starting point for general inflammatory response. Thus it is postulated that flavonoids affect the COX and LOX enzymes to inhibit the release of inflammatory mediators.[5]

EFFECT OF DARK CHOCOLATE ON HUMAN HEALTH

Due to its highly rich cocoa polyphenol content, dark chocolate has been attributed to improve the quality of life of an individual. It is considered to be a good source of medicine for many disorders affecting the human health.

i. EFFECT ON INFLAMMATION

Inflammation is a condition in which the defence system of the body shows an integrated response to a foreign invasion. It involves action of the complement system, blood coagulation, immunity, tissue hormones, angiogenesis and various repair processes. Inflammation involves the process of both free radical generation as well as production.[3] Cycloxygenase (COX) enzymes play a crucial role as inflammatory mediators and are involved in the release of arachidonic acid. This release of arachidonic acid is considered to be the starting point for initiation of an inflammatory response. Thus, the COX enzyme inhibition may relieve the symptoms of inflammation and pain. There are various mechanism by which flavonoids in dark chocolate act in order to fight against inflammation.[13] During inflammation, high concentration of nitric oxide (NO) is produced by inducible *nitric oxide synthase* (i-nos) in macrophages. This NO then reacts with free radicals resulting in oxidative damage to the cell. Since the flavonoids scavenge these free radicals, nitric oxide would no longer be available to interact with free radicals, thus resulting in lesser cellular damage. Flavonoids also inhibit pro-oxidant enzymes which lead to lesser free radical generation. Flavonoids in dark chocolate also inhibit lipopolysaccharide (LPS) induced i-nos gene expression. They also affect the enzyme system involved in the inflammation process. They not only inhibit COX-2 and Lipoxygenase (LOX), but also affect cellular regulation by various *protein kinases* like *protein kinase C* (PKC), *mitogen-activated protein kinase* (MAPK) and *tyrosine protein kinase* (PTK) involved in signal transduction. Inhibition of these enzymes reduce the production of arachidonic acid, prostaglandins (PG), leucotrienes, NO, cytokines which are crucial mediators of inflammation. Through the inhibition of these enzymes, the DNA-binding capacity of transcription factors such as NF-ƙB or activator protein-1 (AP-1) are regulated and the gene expression rate is controlled which leads to the suppression of inflammation. Thus the inhibition of these enzymes by flavonoids present in dark chocolate decrease inflammation.[3,13]

ii. EFFECT ON CANCER

Cancer is caused by disturbance in growth metabolism. Cancer cells manifest to varying degree of uncontrolled proliferation, dedifferentiation and loss of function, invasiveness and metastasis that differ from normal cells. Flavonoids from dark chocolate are now being considered as effector substance. They are recognised as potent bioactive molecules that possess anticarcinogenic effects since they interfere with the initiation, development and

progression of cancer by the modulation of cellular proliferation, differentiation, apoptosis, angiogenesis and metastasis.[1,13,14]

- **Cocoa Polyphenol's Modulation Of Cellular Antioxidant Status**[14]

Cocoa polyphenols have potent antioxidant capacity. A cocoa extract and its main flavonoids exert a protective effect against oxidative stress by various mechanisms. Various studies have been carried out which are enlisted below:

Table No 1: Cocoa polyphenols as antioxidants in cancer treatment

POLYPHENOLS	CONC IN µM	SYSTEM STUDIED	EFFECTS OBSERVED
Epicatechin	12-100	SH-SY5Y (Neuroblastoma)	Decrease in H_2O_2/Fe^{2+} induced ROS production
	1-20	Caco-2 (Colon)	Decrease in acryl amide -induced GSH depletion, and ROS generation
	25-100	MCF-7 (Breast)	Increased CYP1A1 mRNA and protein levels and enzymatic activity, increase binding to XRE
Catechin	10-50	HepG2 (Hepatoma)	Decrease in N- nitrosoamine induced DNA damage

Suppression of cell proliferation and induction of differentiation and apoptosis are important strategies in cancer prevention. Along with these strategies, the induction of programmed cell death is currently considered as one of the relevant target in the preventive approach.

- **Cocoa polyphenol's modulation on cell cycle**[14]

Few of the known hallmarks of cancer are deregulated cell cycle and resistance to apoptosis. Alteration of any cell cycle-specific proteins can affect and/or block the continuous proliferation of cancer cells. In addition, cell cycle checkpoints, such as G1/S and G2/M, are also important targets for cocoa and its polyphenols. Effect of cocoa contents on cell cycle modulation is enlisted below

Table No 2: Effect of cocoa polyphenol on cell cycle

POLYPHENOLS	CONC IN µM	SYSTEM STUDIED	EFFECTS OBSERVED
Polymer procyanidin	0.2-5	Raji (Lymphoma), HL-60 (Leukaemia)	Decrease in Topo II
	50	MDA-MB231 (Breast)	G_0 and G_1 phase arrest
Procyanidin B2	10	LNCaP (Prostate)	Decrease in cell growth
Epicatechin	50-100	HH639 (ovary)	Decrease in cell growth and apoptosis

- **Cocoa polyphenol's modulation on apoptosis process[14]**

Induction of apoptosis may be considered as one of the important targets in a preventive approach against cancer. This programmed-cell death is a complex process that involves the active participation of affected cells in a self-destruction cascade and is defined by a set of characteristic morphological features such as membrane blebbing, shrinkage of the cell and nuclear volume, chromatin condensation and nuclear DNA fragmentation due to endonuclease activation. A synergistic effect has been reported to induce apoptosis by using cocoa phenols. The table enlists various effects of cocoa polyphenols on apoptosis induction.

Table No 3: Induction of apoptosis by cocoa polyphenols

POLYPHENOLS	CONC IN µM	SYSTEM STUDIED	EFFECTS OBSERVED
Polymer procyanidin	2-20	CaCo-2 (Colon)	Decrease Docetaxel induced apoptosis
Epicatechin	30	FEK4 (Skin fibroblast)	Decrease in H_2O_2 induced Caspase-3 activity

- **Cocoa polyphenol's modulation on cell survival and cell proliferation[14]**

The most important signalling pathways regulating cell proliferation and survival involve PI3K/AKT, growth factor receptors/RAS / MAPKs, and NF- κB. Cocoa phenolic compounds can interact with these signalling proteins and modulate their activity.

Table No 4: Cocoa polyphenols' effect on cell proliferation in cancer

POLYPHENOLS	CONC IN µM	SYSTEM STUDIED	EFFECTS OBSERVED
Procyanidin B2	1-20	Caco-2(Colon)	Increase in ERK activity
Procyanidin polymers	17-100	JB6P+ (Epidermal)	Decrease TPA induced neoplastic transformation, decrease in COX-2, regulation of AP-1 and NFκB

- **Cocoa polyphenol's modulation on angiogenesis[14]:** Angiogenesis, the formation and growth of new blood vessels from pre-existing microvasculature is a key stage in tumour growth, invasion, and metastasis. Suppression of angiogenesis can also lend a helping hand in treating cancer.

Table No 5: Effect of cocoa polyphenols affecting angiogenesis

POLYPHENOLS	CONC IN µM	SYSTEM STUDIED	EFFECTS OBSERVED
Cocoa	20	JB6P+ (Epidermal)	Decrease in TNF-induced VEGF, AP-1, NFκB
Epicatechin	1-100	HL-60 (Leukemia)	Decrease in the activity of DNA polymerase and thus affecting angiogenesis

	10	CGR8 (Embryonic stem cell)	Decrease in cell growth, decrease ROS generation thus affecting angiogenesis
Catechin	10-80	B167 (Melanoma)	Decrease in NO, VEGF, IL2,TIMP-1, TNF production, pro-inflammatory cytokines

iii. EFFECT ON THE CARDIOVASCULAR SYSTEM

Flavonoids in dark chocolate have garnered importance in improving cardiovascular system of an individual. They have proved to be beneficial on endothelial function, blood pressure and cardiovascular function. Scientists have studied the effects of cocoa polyphenols on improving endothelial function, delaying the oxidation of LDL cholesterol, lowering blood pressure and improving platelet function.[5,15]

- **Endothelial Function**

Nitric oxide (NO) is a potent vasodilator released by *endothelial nitric oxide synthase* (e-NOS). It allows the arteries and the arterioles to conduct the function of vasodilation. Reduction in the concentration of NO (Nitric oxide) is believed to be the hallmark of endothelial dysfunction. Endothelial dysfunction is attributed with decreased concentration of NO bioavailability due to impairment in NO production or inactivation of NO by reactive oxygen species. It is also associated with the inability of the arteries and arterioles to dilate properly.[10,11] It was studied using isolated rabbit aortic rings that, the extracts of cocoa rich in procyanidin induced endothelium-dependent relaxation as well as increased the activity of e-NOS thus increasing the levels of N.[6,16]

- **Atherosclerosis**

It is a condition manifested by gradual build-up of fatty substances including cholesterol on the walls of the arteries. Decrease in the levels of HDL cholesterol and oxidation of lipids play an important role in the pathogenesis of atherosclerosis. Oxidation of LDL leads to release of various adhesion molecules which lead to plaque formation. This plaque formation reduces the flow of blood to the heart, brain and other tissues resulting in heart attack or stroke It is proved that dark chocolate consumption not only increased the concentration of HDL cholesterol which is referred to as good cholesterol but also increased plasma antioxidant activity. Flavonoids in dark chocolate also helped in decreasing the oxidation of LDL cholesterol and formation of lipid oxidation products.[5,6] It is believed that rather than polyunsaturated fatty acids, it is saturated and monounsaturated fatty acids which inhibit lipid peroxidation. Dark chocolate contains steric acid (saturated fatty acid) and oleic acid (monounsaturated fatty acid) which make the LDL cholesterol more resistant to oxidation and

also reduce the amounts of polyunsaturated fatty acids.[17,18] It is also reported that nitric oxide derived from the endothelium supress the oxidation of LDL cholesterol.[5]

- **Platelet Reactivity**

Platelet reactivity and platelet-endothelial cell interactions are important factors in acute thrombosis development which reflects the cardiovascular health of an individual. Platelet generation and subsequent aggregation leads to atherosclerosis and acute thrombus formation. This thrombogenicity refers to clot formation of blood.[5] *In vivo* studies have revealed that flavanols in dark chocolate have anti-aggregatory effect by inhibition of thromboxane A_2 formation. It is also postulated that NO reduces the stickiness of platelets. There are various other pathways which may modulate platelet functions that prevent stroke, thrombosis and heart attacks.[6,10]

- **Blood Pressure**

Angiotensin converting enzyme (ACE) are said to be involved in regulating blood pressure (BP). ACE converts Angiotensin I to Angiotensin II which is potent vasopressor leading to increase in BP.[19] Inhibition of ACE play an important role in regulation of BP. ACE inhibition will lead to decrease in concentration of Angiotensin II thereby decreasing the consequent activation of *NAD(P)H oxidase*. This will lead to lowering in the levels of *NAD(P)H oxidase* dependent superoxide anions.[19] Researchers investigated that the peptide content in dark chocolate lead to decrease in BP. It is the high amount of hydrophobic amino acids in cocoa that contribute to the ACE inhibitory and antioxidant activity. This ACE inhibition led to proper maintenance of blood pressure.[20] Studies have also revealed that dark chocolate rich in phenolic compounds lead to the increase in bioavailability of NO which bring about BP regulation and improve endothelial function.[11,19,20]

iv. EFFECT ON CENTRAL NERVOUS SYSTEM:

- **Effect of Dark Chocolate on Sexual Arousal, Mood Lifting and Stress**

Dark chocolate is said to have several effects on human sexuality. It act as an aphrodisiac which lead to increased sexual desire and improved sexual pleasure. It is claimed that, the substance responsible for this phenylethylamine which help in the stimulation of hypothalamus, thus increasing the levels of endorphins and 5-HT *i.e.* 5 hydroxy tryptamine also known as the happy hormone. Endorphins are substances released in the body to reduce pain and stress. This brings about mood lifting and feelings of euphoria in men and women.[1]

Dark chocolate also contain methyl xanthines like theobromine and caffeine which act as stimulants to increase alertness. They compete with adenosine, a pre-synaptic inhibitory modulator and block its receptor thus bringing in mental and physical relaxation.[21]

An interesting substance found in dark chocolate which is associated with chocolate craving is Anandamide. Anandamide has a structural analogy with tetrahydrocannabinol found in marijuana. It activates cannabinoid B_1 receptors in the brain leading to the stimulation of dopamine pathway which causes extracellular dopamine release in the nucleus accumbens region of the brain resulting in euphoric state and increased pleasure. Thus, dark chocolate is associated with good and high feeling.[1, 22]

- **Effect on Neuro-degenerative disorders**

There is an alarming evidence that flavonoids in dark chocolate improve the brain function and help keep dementia and Alzheimer at bay.[23] Researchers have found that consuming flavonoid rich dark chocolate helped improve mild cognitive impairment which is a condition involving memory loss leading to dementia and Alzheimer's disease. Flavonoids present in dark chocolate have an inhibitory action on the development of Alzheimer's disease.[3] They show interaction with cellular cascades like MAPK, ERK and PI3 kinase/AKT pathway and increase the expression of brain derived neurotropic factor (BDNF) and other neuromodulatory and neuroprotective proteins.[23] This bring in changes in synaptic plasticity and promote neurogenesis and help in neuron survival which in turn leads to increase in the long term potentiation and memory formation that altogether improve cognitive function.[12, 24,25]

v. EFFECT ON GLUCOSE METABOLISM

- **Effect on insulin sensitivity**

Cardiovascular risk and impairment of insulin sensitivity have a very close connection via mutual dependence on the bioavailability of NO.[18] Conditions of hyperglycaemia result in increase in oxidative stress in beta cells of islets of Langerhans in the pancreas which further promotes insulin resistance and impairment of endothelium-dependent vasodilation.[26] Flavanols and other polyphenolic antioxidants in dark chocolate improve the insulin resistance by increasing the endothelial bioavailability of NO and decreasing the activity of reactive oxygen species.[26,27] Studies were carried out to check the effect of flavanol-rich dark chocolate and flavanol-free chocolate bars on glucose and insulin responses using the

oral glucose tolerance test (OGTT) and it was concluded that insulin sensitivity is partly dependent on NO bioavailability in the endothelial cells.[26]

- **Effect on Diabetes Mellitus**

Diabetes Mellitus is a serious chronic disorder manifested by increase in blood glucose levels. Since most of this disease is genetic, there are few polyphenols which can curb diabetes. Flavonoids have been identified as good inhibitors of *aldose reductase,* a cytosolic NADPH-dependent *oxido-reductase* that catalyses reduction of glucose to sorbitol which is considered to be the first step in polyol pathway of glucose metabolism. It has been reported that quercetin possess anti diabetic activity and help in regeneration of pancreatic islets, thus, increasing insulin release in streptozotocin-induced diabetic rats.[3,5,27]

vi. EFFECT ON ORAL HEALTH

Dental plaque formation plays a very crucial role in the development of caries and periodontal diseases in humans. The carbohydrate substrate that we consume break down into starch and sucrose. Dextransucrase enzyme *i.e.* 6-*glucosyltranferase* is the enzyme which further breaks down sucrose into various extracellular polysaccharides like glucan, fructan *etc.* these substances form dental plaque around the teeth which on accumulation convert into lactic acid. This lactic acid may lead to enamel dissolution and various periodontal diseases. The production of caries and chocolate consumption are often cited in literature considering the fact that, chocolate consumption is detrimental for tooth health. Researchers state that there are possible protective effect of cocoa polyphenols present in the dark chocolate on dental caries. The phenolic substances in dark chocolate are considered as inhibitors of the 6-*glucosyltranferase.* Studies also reveal that a water soluble extract of cocoa powder significantly reduce caries score in rats infected with *streptococcus sobrinus*, a potent cariogenic agent. Periodontal tissue destruction may take place when there is a disequilibrium between oxidative stress and anti-oxidant activity. Studies have revealed that cocoa enriched diet has proven to be beneficial on gingival oxidative stress in rat periodontitis model. Cocoa polyphenols showed diminished periodontitis-induced oxidative stress, which in turn, might supress the progression of periodontitis.[3,28]

CONCLUSION

The above mentioned effects are conclusive proof that, dark chocolate is not only a delicious delicacy but also an effective therapeutic agent. These fact can be considered for introspection of dark chocolate as an emerging therapeutic drug in the field of medicinal

science. Anti-oxidant property of cocoa polyphenols is highly important for maintenance of good health and for this 100 grams of dark chocolate is to be consumed every day. Thus it is rightly said that, when you select the right type of chocolate, it is like giving your insight a hug and everyone needs a tempting dark chocolate hug.

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