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A REVIEW OF THE EFFECTIVENESS NATURAL PIGMENT AS ANTIDIABETIC TO DECREASE THE SIGNIFICANT RISK FOR COVID-19 DISEASE

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ABSTRACT

Diabetes mellitus proved to be a significant risk factor for both COVID-19 infection and poor outcomes among these chronic health problems. Plants are a rich source of chemical components that could block carbohydrate digestion enzymes, and they can be utilized as therapeutic or functional foods. Natural pigments that have potential benefits, such as chlorophyll, anthocyanin as a part of flavonoid, and carotenoid. Chlorophylls are the most significant and widespread pigment molecules in nature, and they are required for photosynthesis to occur. Anthocyanins are the most important group of water-soluble pigments in plants, responsible for the red, purple, and blue colors of many fruits, vegetables, cereal grains, and flowers. Carotenoids, natural pigments found in an array of different foodstuffs, are the most abundant pigments present in the human diet. The most frequent method for determining a substance's antidiabetic potential is to assess the substance's hypoglycemic or antihyperglycemic.

Keywords: anthocyanin; antidiabetic; chlorophyll; carotenoid; natural pigment

ABSTRAK

Diabetes mellitus terbukti menjadi faktor risiko yang signifikan untuk infeksi COVID-19 dan dampak buruk di antara masalah kesehatan kronis lainnya. Tumbuhan merupakan sumber yang kaya akan komponen kimiawi yang memiliki kemampuan untuk memblokir enzim pencernaan karbohidrat, sehingga dapat dimanfaatkan sebagai makanan terapeutik ataupun fungsional. Pigmen alami yang memiliki potensi manfaat antara lain klorofil, antosianin sebagai bagian dari flavonoid, dan karotenoid. Klorofil adalah molekul pigmen yang paling signifikan dan tersebar luas di alam, dan pigmen ini diperlukan untuk terjadinya fotosintesis. Antosianin adalah kelompok pigmen larut air yang paling penting pada tumbuhan, yang bertanggung jawab atas warna merah, ungu, dan biru pada banyak buah, sayuran, biji-bijian sereal, dan bunga. Karotenoid adalah pigmen alami yang ditemukan dalam berbagai bahan makanan yang bervariasi, sebagai pigmen paling melimpah yang ada dalam makanan manusia. Metode yang paling sering digunakan untuk menentukan potensi antidiabetes suatu zat adalah dengan menilai hipoglikemik atau antihiperglikemik dalam kandungan tersebut.

Kata kunci: antosianin; antidiabetes; karotenoid; klorofil; pigmen alami

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INTRODUCTION

A novel coronavirus, the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was discovered in Wuhan (Hui et al, 2020). Although the virus affected people of all ages, it was more common in elderly people, especially those who had underlying chronic health issues. Diabetes mellitus, in particular, proved to be a significant risk factor for both COVID-19 infection and poor outcomes among these chronic health problems. Diabetes is already linked to an increased risk of death from any acute or chronic disease, including infection (Zoppini et al, 2018). At least one comorbidity was found in 25.1% of COVID-19 patients in a Chinese national study of 1,590 hospitalized patients. Hypertension (16.9%) was the most common comorbidity, followed by diabetes (8.2%) (Guan et al., 2020).

Plants are a rich source of chemical components that have the ability to block carbohydrate digestion enzymes, and they can be utilized as therapeutic or functional foods (Sales et al., 2012). Oxidative stress, on the other hand, is one of the most common issues in diabetes patients, and it can lead to serious consequences. As a result, one of the goals for creating next-generation antidiabetic medicines is to locate antidiabetic compounds or extracts with antioxidant properties (Orhan et al., 2020).

In this review, there are several types of research that can be evaluated as new natural sources in the treatment of diabetes mellitus, especially for the natural pigments that have potential benefits, such as chlorophyll, anthocyanin as a part of flavonoid, and carotenoid. Chlorophyll is chosen because this natural pigment is the largest. Anthocyanin is also reviewed as a water-soluble pigment in nature that is very abundant. Chlorophyll and anthocyanin are found in plants, but carotenoids can be found both in plants as well as animals that are very abundant in the human diet. These three pigments have significantly bioactive compounds such as antidiabetic also be functional foods nowadays.

DIABETES MELLITUS

Diabetes mellitus (DM) is a metabolic disease characterized by excessive blood sugar, dyslipidemia (impaired lipoprotein metabolism), and altered protein metabolism as a result of decreased insulin production and/or action. Diabetes mellitus (DM) is a condition marked by persistently high blood sugar (hyperglycemia) caused by a lack of insulin synthesis, secretion, or resistance. This condition is critical since the number of sufferers is growing, it is estimated that there are presently 200 million sufferers worldwide. Furthermore, DM is critical due to the problems it creates. The majority of chronic consequences of DM are caused by vascular diseases, namely tiny blood vessels (microangiopathy) and big blood vessels (aneurysms) (macroangiopathy) (Kariadi, 2001). Type 1 diabetes mellitus (DM-1) is also known as insulin-dependent diabetes mellitus (IDDM), while type 2 diabetes mellitus (DM-2) is also known as noninsulin-dependent diabetes mellitus (NIDDM).

Insulin production is nonexistent or limited in DM-1 severe pancreatic damage, thus insulin must be obtained from outside the body. DM-1 is also known as insulin-dependent diabetes mellitus, and it can strike at any age (children, adolescents). Insulin insufficiency is present in DM-2, although it is not as severe as it is in DM-1. Insulin resistance is associated with insulin insufficiency in DM-2, meaning that the presence of insulin is unable to control blood sugar levels adequately for the body's demands, and so plays a role in raising blood sugar levels. DM-2 generally manifests itself at the age of 30-40 years, and it can even manifest itself at the age of 50 or 60 years. The most frequent method for determining a substance's antidiabetic potential is to assess the substance's hypoglycemic or antihyperglycemic (blood sugar lowering) impact in experimental animals, generally rats with alloxan-induced diabetes. Due to damage to the β-cells of the islets of Langerhans in the pancreas, alloxan induces a significant reduction in insulin excretion, resulting in hyperglycemia (Marpaung, 2020). Several phytochemicals potentially use to change to hypoglycemic such as chlorophyll, anthocyanin, and carotenoid.

NATURAL PIGMENT AS ANTIDIABETIC

Plants have three mechanisms of reducing blood sugar levels. First, it acts as an astringent, which means it may precipitate intestinal mucous membrane proteins and produce a protective barrier around the intestines, preventing glucose absorption and lowering blood glucose levels. Second, it accelerates the release of glucose from the circulation by accelerating blood circulation, which is closely related to the work of the heart, as well as filtration and renal excretion, resulting in increased urine production, increased glucose excretion through the kidneys, and lower blood glucose levels. Third, increased metabolism or incorporation into fat deposits speeds up the release of glucose. The pancreas is involved in this process because it produces insulin (Suryowinoto, 2005). The importance of reducing postprandial hyperglycemia (PPHG) in the treatment of type 2 diabetes has been demonstrated by a favorable connection between human pancreatic alpha-amylase (HPA) activity and the increase in postprandial glucose levels (Watanabe et al., 1997). The capacity of alpha-amylase enzyme inhibitors to prevent dietary starch from being digested and absorbed in the body has led to the label "starch blocker" (Horii et al., 1986).

Besides, antioxidants in the form of vitamins can help patients with DM-1, both chronic and acute, minimize oxidative stress (Lee, 2002). The majority of antioxidants in plasma can be decreased in individuals with DM-2 as a result of diabetic complications such as atherosclerosis and coronary heart disease (Tiwari & Rao, 2002). Insulin resistance can be greatly improved by taking 132 mg of isoflavones from soybean extract every day for 12 weeks. Consumption of high-carotene vegetables and fruits can protect against hyperglycemia, and plasma levels of lutein and β-carotenoids can help healthy volunteers maintain blood glucose levels indirectly. In DM-2 test animals, carotenoids and astaxanthin can lower non-fasting blood glucose levels. Grape seed extracts include a number of flavonoids, notably proanthocyanidins, which can improve insulin sensitivity and decrease free radical production. The flavonoid quercetin was discovered to be effective in preventing the development of diabetic cataracts (Schoenhals, 2005).

CHLOROPHYLL

Chlorophylls are the most significant and widespread pigment molecules in nature, and they are required for photosynthesis to occur. They serve a crucial part in photosynthesis by absorbing, transmitting, and transducing light energy (Scheer, 2006). Chlorophyll is a blue or green pigment that has a maximum absorption range of 660 to 665 nm. (Hosikian et al, 2010). It is required for photosynthesis because it allows charged electrons to flow through to molecules that produce sugars. All-natural chlorophyll derivatives have a centrally attached magnesium atom and are substituted tetrapyrroles (Ferruzzi & Blakeslee, 2007). The abundant availability of chlorophyll in nature, as well as its biological characteristics, have made it a viable candidate for development as a dietary supplement or functional food (Prangdimurti, 2007). Meanwhile, nearly all chlorophyll-based dietary supplements on the market in Indonesia are imported and sell for a relatively high price (Nurdin et al., 2009).

Chemical structure

Chlorophylls may be classified into two groups based on their distribution in photosynthetic organisms: chlorophylls in oxygenic photosynthetic organisms (abbreviated Chls) and chlorophylls (bacteriochlorophyll) in anoxygenic photosynthetic bacteria (abbreviated BChls) (Chew and Bryant 2007). For a long period, it was believed that there are only four chemically distinct chlorophylls in oxygenic photosynthetic organisms, namely Chls a, b, c, and d (Chen et al., 2010). Plants also contain tiny quantities of pheophytin, protochlorophyllide, and other compounds in addition to Chls and BChls. Chlorophylls are cyclic tetrapyrroles with a distinctive isocyclic five-membered ring (porphyrin ring) that are used in photosynthesis for light-harvesting or charge separation. The structure can be seen in Figure 1. Chlorophyll members have varied characteristics depending on their architectures, allowing different photosynthetic organisms to adapt to different conditions. The IUPAC-IUB nomenclature is used to name the rings and carbon atoms on a chlorophyll structure (Moss, 1988).

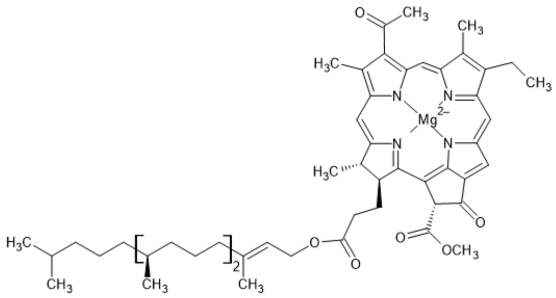

Figure 1. Chlorophyll general structure

Green algae contain chlorophyll b, a green or yellow pigment with a maximum absorption range of 642 to 652 nm. Chlorophyll b is an auxiliary pigment that absorbs light and transfers it to chlorophyll a during photosynthesis (Hosikian et al., 2010). Chlorophyll c is a blue-greenish pigment that has a maximum absorbance range of 447 to 452 nm. Chlorophyll c can also be present in seaweed. Chlorophyll d is found in red algae and marine cyanobacteria, and it absorbs far-red light with a wavelength of 710 nm (Larkum & Kühl, 2005). Porphyrins, chlorins, bacteriochlorins, pheophorbides, bacteriopheophorbides, texaphyrins, porphycenes, and phthalocyanines are some of the types of chlorophyll produced from marine algae and cyanobacteria. These derivatives exhibit chlorin's basic structural skeleton and absorb light significantly in the red band spectrum (Li et al., 2007).

Chlorophyll sources

Chlorophyll is the most significant tetrapyrrolic pigment, found in sea algae and cyanobacteria as part of a chlorophyll-protein complex (Hosikian et al., 2010). Besides, chlorophyll pigment can be found in several types of plants. According to Ashok (2011), a project is underway to demonstrate the effectiveness of wheatgrass in the treatment of diabetes mellitus. *Triticum aestivum* L. is an immunomodulator, antioxidant, astringent, laxative, diuretic, and antibacterial plant that is used in the treatment of acidity, colitis, renal dysfunction, swollen wounds, and vitiated states of the Kapha and Pitta doshas.

Wheatgrass is also thought to have the ability to regulate blood sugar levels. The existence of chlorophyll, which is thought to be a pharmacologically active component in wheatgrass as an antidiabetic drug, was verified by instrumental characterization of wheatgrass (spray-dried powder of juice). Chlorophyll a has a maximum of 661.1, whereas chlorophyll b has a maximum of 642.6. The GC-MS results revealed peaks linked to chemicals that are chlorophyll degradation products. Furthermore, HPLC examination confirmed the existence of chlorophyll a and chlorophyll b.

The pigment content of acetone and ethanol extracts of *G. salicornia*, *T. decurens*, and *H. macroloba* revealed that the green algae *H. macroloba* had the highest content for all types of pigments, with chlorophyll C1+C2 being the pigment with the highest content, with values of 1.85±0.53 and 6.23±0.12 mg/g dry weight for the acetone and ethanol extracts, respectively (Sanger et al., 2018).

Chlorophyll as antidiabetic

In recent years, chlorophyll derivatives have opened a slew of new possibilities for photodynamic treatment (Li et al., 2007). Antibacterial (Alenezi et al., 2017), antioxidant (Lanfer-Marquez et al., 2005), anti-inflammatory (Jelic et al., 2012), and antimutagenic activities (Ferruzzi & Blakeslee, 2007) are all common uses for chlorophyll derivatives in biomedical applications.

According to Shilpa Vs et al. (2019), fresh *E. hirta* leaves were nutritionally analyzed and found to possess adequate quantities of essential components. With an IC_{50} value equivalent to that of the medication metformin, this plant demonstrated considerable inhibition of the enzyme alpha-amylase in a concentration-dependent manner, suggesting that it may yield important antidiabetic chemicals for use in the treatment of diabetes. Antidiabetic efficacy of *Euphorbia hirta* was investigated using an in vitro alpha-amylase inhibition test.

The methanolic extract of *Euphorbia hirta* was found to have concentration-dependent inhibitory action against the α-amylase enzyme, with an IC_{50} of 0.748 mg/ml in this investigation. The extract's in vitro antidiabetic efficacy was compared to that of the standard medication Metformin, which has an IC_{50} of 0.58 mg/ml. Since *E. hirta* methanolic extract has an IC_{50} value that is equivalent to that of the conventional medication, it inhibits alpha-amylase significantly, and therefore it may have antidiabetic potential. Other Euphorbiaceae plants, such as *Phyllanthus amarus*, *Acalypha indica*, and *Euphorbia thymifolia*, have been found to have considerable antidiabetic potential through their inhibition of the alpha-amylase enzyme.

The antioxidant activity of *G. salicornia* acetone extract was measured at IC_{50} of 1.24±0.1402 mg/mL. *G. salicornia* possesses antioxidant, ion-reducing, chelating, cytotoxic, and antidiabetic properties (Sanger et al. 2013; Saeidnia et al. 2009). According to Hardoko et al. (2015), *G. gigas* includes agarose (0.28%), agar (5.91%), and agaropectin (6.07%), all of which exhibit antidiabetic action by reducing the activity of the α-glucosidase enzyme with IC_{50} values of 0.09±0.004, 0.12±0.005, and 0.15±1.77 mg/mL, respectively.

In alloxan-induced diabetic mice, a dosage of 150 mg/kg of *Clinacanthus nutans* leaf water extract can lower blood glucose levels. This supports its usage as an antidiabetic in the population. When compared to the other fractions, the ethanol precipitate fraction contained the same secondary metabolite compounds as the aqueous extract, namely flavonoids, steroids/triterpenoids, and tannins, which resulted in the greatest reduction in blood glucose levels in mice using the glucose tolerance method (Nurulita et al., 2008).

Adding alfalfa seed to the human diet has been shown to lower triglycerides and LDL, enhance HDL levels, and lower blood glucose levels in previous studies (Asgary et al., 2008; Mehranjani et al., 2008). As a result, alfalfa leaves have long been utilized in South Africa as an effective diabetic therapy (Lust, 1986; Gray & Flatt, 1997). Insulin secretion is stimulated by alfalfa. It also enhances insulin function by lowering blood glucose levels, although its effects on blood lipids have not been well studied (Gray & Flatt, 1997; Winiarska et al., 2007). Fourty experimental rats were randomly divided into four groups, each with ten rats: first, a control group fed normal water and food; second, a diabetic control group; third, an experimental group consisting of diabetic rats given a 250 mg/kg dose of alfalfa aqueous extract; and fourth, a diabetic group consisting of diabetic rats given a 500 mg/kg dose of alfalfa aqueous extract; and fourth, a diabetic group consisting The remaining three diabetic groups were produced by injecting 120 mg/kg alloxan monohydrate intraperitoneally to produce alloxan-induced diabetic rats (Matkovics et al., 1997).

Blood glucose of rats was tested seven days after alloxan monohydrate injection for confirming the diabetic condition in rats, and diabetic rats with blood glucose concentrations more than 200 mg/100 cc were chosen (8 rats out of 10) (Takasu et al., 1991). For equivalence of shock achieved by intraperitoneal injection, the first control group is injected with the physiologic serum. To easily comparing the research respectively, these all experiments compile into Table 1 below.

ANTHOCYANIN

Chemical structure

Anthocyanins are efficient hydrogen donors. Anthocyanins can easily donate protons to highly reactive free radicals, preventing further radical formation, due to their positive charge (Figure 1), the number and arrangement of aromatic hydroxyl groups, the extent of structural conjugation, and the presence of electron-donating and electron-withdrawing substituents in the ring structure (Oliveira et al., 2020).

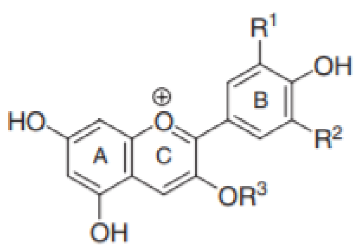

Figure 2. General anthocyanin structure present in fruits (Freitas and mateus, 2006; Kähkönen and heinonen, 2003; Giusti et al., 1999).

Table 1. Effectiveness chlorophyll as antidiabetic in several research

Sources	Extraction	Mechanism	Experiment	Reference
Fresh *Euphorbia hirta* leaves	Methanol	Inhibitory action against the α-amylase enzyme	In vitro	Shilpa Vs et al. (2019)
Gracilaria gigas	Ethanol (agar), Dimethyl sulfoxide (agarose & agaropectin)	Reducing the activity of the α-glucosidase enzyme	In vitro	Hardoko et al. 2015
Clinacanthus nutans leaf	Water	Alloxan-induced diabetic mice	In vivo	Nurulita et al., 2008
Alfalfa seed	Aqueous	Fourty experimental rats were randomly divided into four groups	In vivo	Matkovics et al., 1997; Takasu et al., 1991

Because of their peculiar chemical structure, anthocyanins possess health properties. They are reactive towards reactive oxygen species (ROS), such as superoxide ($O2^{\cdot-}$), singlet oxygen ($^1O_2$), peroxide ($RCOO^{\cdot}$), hydrogen peroxide (H_2O_2), and hydroxyl radical ($OH^{\cdot}$), as well as reactive nitrogen species in a terminator reaction, which breaks the cycle of generation of new radicals, due to their electron deficiency (Magalhaes et al., 2008; Choe and Min, 2006; Kong et al., 2003; Min and Bolf, 2002). The antioxidant properties of phenolic compounds are also linked to chelate metal ions, which participate in the generation of free radicals and so reduce metal-induced peroxidation (Liu, 2010). Anthocyanins exhibit multiple biological effects, but this paper will focus on the antidiabetic effect.

Anthocyanins are glycosilate polyhydroxy or polymethoxy derivatives of 2-phenylbenzopyrilium with molecular weights ranging from 400 to 1200 (medium-size biomolecules) and two benzyl rings (A and B) (Andersen and Jordheim, 2010; He and Giusti, 2010; Castaneda-Ovando et al., 2009; Gould et al., 2009; Ghosh & Konishi, 2007). Anthocyanins are most commonly found as glycosides. The aglycones are rarely found in plants other than as artifacts; the 3-deoxy forms, which can be found in red-skinned bananas, sorghum, and black tea, are the notable exceptions. The sugars most commonly encountered are glucose (the most common), galactose, rhamnose, arabinose, xylose, and glucoronic acid, usually as 3-glycosides or 3.5-diglycosides (Pereira et al., 2009; Freitas and Mateus, 2006); 3-diglycosides and 3-diglycoside-5-monoglycosides are less common. Rutinose, sambubiose, lathyrose, and sophorose are the four main biosides encountered. In terms of glycoside distribution, 3-glycosides occur almost two and a half times as frequently as 3.5-diglycosides, with cyanidin-3-glucoside being the most common anthocyanin (Kong et al., 2003). Anthocyanidins are the de-glycosilated or aglycone forms of anthocyanins.

Anthocyanin sources

Anthocyanins are naturally occurring pigments. Throughout the plant kingdom, it can be found in all plant tissues (Kong et al., 2003). Anthocyanins are phytochemicals that belong to the flavonoid family and are found in nature (Pervaiz et al., 2017). Anthocyanins belong to the phenolics or polyphenolics superfamily of antioxidants (Quideau et al., 2011; Ferretti et al., 2010; Daayf and Lattanzio, 2008). Flavonoids are a class of phytochemicals that make up the most important category of phenolics in foods. They are commonly found in teas, honey, wines, fruits, vegetables, nuts, olive oil, cocoa, and cereals (Raghvendra et al., 2011; Wallace, 2011; Andersen & Markham, 2006).

Anthocyanins are the most important group of water-soluble pigments in plants, responsible for the red, purple, and blue colors of many fruits, vegetables, cereal grains, and flowers. They are odorless and practically flavorless, adding to taste as a somewhat astringent sensation (He & Giusti, 2010; Gould et al., 2009; Motohashi, 2008; Veitch and Grayer, 2008; Andersen & Jordheim, 2006; Escribano-Bailón et al., 2004; Vidal et al., 2004; Williams and Grayer, 2004; Harborne & Williams, 2000; Harborne & Grayer, 1988). Anthocyanins obtained from fruits and vegetative tissues have simpler structures than anthocyanins isolated from flowers (Andersen & Jordheim, 2010).

Anthocyanin as antidiabetic

Diabetes mellitus is a disease with an oxidative stress component. Free radicals react with biomembranes causing oxidative destruction of unsaturated fatty acids to form cytotoxic aldehydes via lipid peroxidation. Furthermore, lipid peroxidation was measured under conditions of thiobarbituric acid reactive substances (TBARS) and lipid hydroperoxides (HPX), which are the end products of lipid peroxidation. Increased lipid peroxidation of membranes and lipoproteins occurs in patients. HPX formed from lipid peroxidation has a direct toxic effect on endothelium cells and degrades to form hydroxyl radicals. This can be seen in beta pancreatic cells (Pari & Latha, 2005).

Free radicals are unstable, reactive, and have the ability to damage biological molecules so that free radicals in excess in the body are very dangerous because they cause damage to cells, nucleic acids, proteins, and fatty tissues. Free radicals are formed in the body as a by-product of metabolic processes or because the body is exposed to free radicals through breathing (Tias, 2010). The normal body contains endogenous antioxidant or anti-free radical mechanisms. Antioxidants are compounds that can inhibit free radical reactions in the body (Wardatun, 2011). Antioxidants can stop the process of cell destruction by donating electrons to free radicals. Antioxidants will neutralize free radicals so they do not have the ability to steal electrons from cells and DNA. The mechanism of action of primary antioxidants is to prevent the formation of new free radical compounds or change the free radicals that have been formed to become more stable and less reactive by breaking the chain reaction (polymerization) or known as chain breaking (Sayuti and Yenrina, 2015).

The flavonoid group of compounds has been reported to have antioxidant activity. Anthocyanins are included in the flavonoid group, namely compounds that function as antioxidants because these compounds are phenolic compounds with an -OH group attached to the carbon of the aromatic ring. Antioxidants block reactive oxygen species (ROS) that damage DNA and cause mutations. The free radical product of this compound is resonance stabilized and is not reactive when compared to other free radicals so that it can function as an antioxidant (Budiarti et al., 2014).

These anthocyanins can lower blood sugar levels by increasing insulin resistance, protecting beta cells, increasing insulin secretion, and reducing glucose digestion in the small intestine. Its mechanism of action is related to its antioxidant properties, but enzymatic prevention and other means are also relevant (Sancho and Pastore, 2012). Antioxidant activity is able to capture free radicals that cause pancreatic beta-cell damage and inhibit pancreatic beta-cell damage so that the remaining beta cells still function. These antioxidants are thought to be able to protect a number of beta cells that remain normal, thus enabling the regeneration of the remaining beta cells through the process of mitosis or through the formation of new islets by endocrine proliferation and differentiation of ductal and ductular cells (Suryani et al., 2013). However, to achieve an effect in a particular tissue, the bioactive compound must be available i.e. effectively absorbed from the intestine into the circulation and delivered to the appropriate area to reach the target. Fruits rich in anthocyanins, extracts or pure compounds have been shown to be effective in preventing or suppressing diseased areas (Miguel, 2011).

CAROTENOID

Chemical structure

Carotenoids, natural pigments found in an array of different foodstuffs, are the most abundant pigments present in the human diet (Ngamwonglumlert & Devahastin, 2019). They are lipid-soluble and show a range of reds, oranges, and yellows, and are divided into 2 groups, which are carotenes and xanthophylls. Carotenes are hydrocarbons, with xanthophylls being their oxygenated counterparts (Campbell-Platt and IUFoST, 2017). There are over 600 different carotenoids, but this paper will focus only on 5 of them, that being lutein, β-Carotene, lycopene, zeaxanthin, and astaxanthin.

In the human diet, carotenoids are mainly found in fruits and vegetables, though they also appear in some animal tissues and products, such as salmon and egg yolk. The name itself is a clue as to the most well-known source of carotenoids; that being carrots, where they give carrots their orange coloring. Although, carotenoids are also available from leafy greens such as kale, spinach, and lettuce, and other sources, like in tomatoes, where the red pigment is a result of the presence of lycopene, a red-colored carotenoid (Schieber & Weber, 2016; Ngamwonglumlert & Devahastin, 2019). All of these things are commonly present in the average diet.

The general structure of carotenoids grants them their colorings. They usually have a 40-carbon chain backbone, with 8 isoprene molecules, and multiple double bonds. The differences between the colors occur due to differences in the full structure. (Ellison, 2016) Some examples of the structure of a few carotenoids are shown in Figure 3 below.

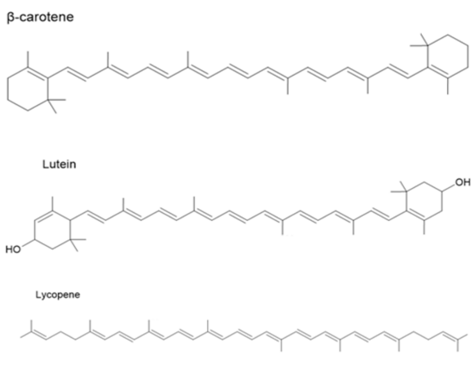

Figure 3. Several carotenoids structures

Carotenoids have been observed to have many positive effects on human health. The most studied of which being their antioxidative properties, and link to eye health. Some of them (such as β-carotene) are provitamin A, meaning they're easily converted into vitamin A, which is essential for the proper function of the immune system (Krinsky & Johnson, 2005). There is even evidence of carotenoids having positive effects against cancer, but this paper will be focused on the 6 mentioned possible effects of carotenoids regarding diabetes and glucose intolerance, and complications that can arise from such.

Carotenoid as antidiabetic

Since carotenoids are antioxidants and diabetes is a disease that is brought on by oxidative stress, the possibility of carotenoids having a role in the fight against diabetes has been speculated on for a while. Limited studies have been done on the subject, and the few that have been done have produced mixed results. Each of the selected carotenoids will be looked at separately.

β-Carotene

β-Carotene, a red-orange pigment found in carrots, sweet potatoes, and other fruits and vegetables, is one of the most common carotenes available, with it being abundant in the human diet (Schieber & Weber, 2016). It is the most commonly studied carotenoid, with health benefits being widely known at this point. Benefits of β-Carotene for the prevention of diabetes have been suggested many times, though until recently, there has not been solid evidence regarding such.

A study (Sluijs et al., 2015) done over 10 years and released in 2015 concluded that, among 37,846 people, higher consumption of β-Carotene does contribute to lowered risk of diabetes. Other, smaller studies have also found an association between β-Carotene and lowered risk of diabetes (Montonen et al., 2004; Ärnlöv et al., 2008; Asemi et al., 2016). β-Carotene is considered a strong antioxidant, which is generally attributed to its benefits against diabetes, as antioxidants reduce oxidative stress, the base cause of diabetes.

There is evidence that β-Carotene is also beneficial for those already afflicted with diabetes. Some studies (Canas et al., 2012; Asemi et al., 2016) have observed that consumption of β-Carotene by individuals with type 2 diabetes has benefits towards insulin metabolism.

Lycopene

Lycopene is another one of the major dietary carotenoids. It exhibits a red color and is most found in tomatoes, watermelon, and other red or orange-red fruits, though it is mostly associated with tomatoes and tomato products (Rao et al., 2006). Unlike β-Carotene, lycopene is a non-provitamin A carotenoid (Ellison, 2016).

Lycopene has been observed to reduce oxidative stress, which is perceived to play a part in the prevention of the development of type 2 diabetes and the alleviation of its complications. A few studies have been conducted to find a solid connection, though results are generally inconclusive. Some studies yielded results suggesting that higher lycopene intake reduces the risk of diabetes (Sugiura et al., 2015), but the margins were not significant. Other studies show that there is no association with lycopene and lowered diabetes risk or prevention at all (Wang et al., 2006). The interest in lycopene's role in human health is more focused towards other diseases such as cancer rather than diabetes, so not many studies have been done.

Lutein

A xanthophyll (that is, an oxygenated carotenoid) carotenoid that is available in egg yolks, corn, carrots, and fish, lutein is one of the major dietary carotenoids. It is yellowish in color, and along with β-Carotene, lycopene, and zeaxanthin, is one of the most common carotenoids present in the human diet (Abdel-Aal et al., 2013).

The role of lutein in eye health is well documented (Koushan et al., 2013; Abdel-Aal et al., 2017; Mitra et al., 2021), though its potential benefits against diabetes itself has limited research, and what research was conducted yielded inconsistent results (Sluijs et al., 2015; Sugiura et al., 2015). However, it has been documented that lutein helps alleviate complications caused by diabetes, particularly when it comes to the eyes, such as with diabetic retinopathy (Hu et al., 2011). A study was also done on diabetic rats that concluded that lutein might also help prevent the development of diabetes related cataracts (Arnal et al., 2009).

Zeaxanthin

Zeaxanthin is a xanthophyll that is yellow in color, found in eggs and squash and an array of other foodstuffs (Tudor & Pintea, 2020). It is not as abundant as some of the other carotenoids mentioned in this paper, but its effect on health has more often been studied thus far compared to other carotenoids, excluding perhaps β-Carotene. Its effects are often studied alongside lutein, as they are isomers of each other, with both being commonly related to protection against several eye diseases, among other things (Ribaya-Mercado & Blumberg, 2004).

The role of zeaxanthin specifically in the prevention of diabetes itself has not been investigated all that often, however more general studies of the association between carotenoids and risk of type 2 diabetes have yielded conflicting results. Some report an inverse relationship between zeaxanthin intake and cases of diabetes (Montonen et al., 2004; Coyne et al., 2005), while others remain inconclusive (Sluijs et al., 2015).

Astaxanthin

Astaxanthin is a xanthophyll that, unlike its counterparts previously discussed, are commonly present in salmonid and crustaceans, where astaxanthin gives them their red orange coloring (Higuera-Ciapara, Félix-Valenzuela and Goycoolea, 2006). It was chosen to be included in this paper because it is a somewhat common animal sourced carotenoid, as well as its associations with diabetes alleviation and prevention.

CONCLUSION

The COVID-19 pandemic, which has been ongoing since December 2019, has caused many deaths.

Diabetes mellitus proved to be a significant risk factor for COVID-19 infection. Studies have shown that natural pigments from plants possess many health benefits especially as diabetes mellitus patients with their phytochemicals. These pigments, namely chlorophylls, anthocyanins, and carotenoids exhibit antidiabetic properties, with different working mechanisms. Furthermore, potential bioactive compounds also containing in these natural pigments are very abundant in nature and human diet. Some researchers are be done with in vitro and in vivo analysis to give the proofs about the effectiveness of natural pigments as antidiabetic substances. This potential should be utilized properly through the exploration of natural pigments for practical applications in food or for commercialization in industrial forms. Although natural pigments have a weakness, namely the color is not uniform, and tends to be expensive. However, natural pigments have the advantage of being food coloring which tends to be safe compared to synthetic dyes and is also beneficial for human health as functional food.

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