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A Systematic Review on Betalain

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Abstract.

Betalains are a group of water-soluble pigments found in certain plants, particularly in the order Caryophyllales, which includes beets, cactus, and amaranth. They are responsible for the bright red-violet and yellow-orange colors of these plants. Betalains are divided into two groups: betacyanin's, which are the red-violet pigments, and betaxanthins, which are the yellow-orange pigments. These pigments are distinct from other plant pigments such as anthocyanins and carotenoids. Betalains have been found to have potential health benefits, such as anti-inflammatory and antioxidant properties. They have also been studied for their potential as natural food colorants and in the treatment of certain diseases. However, Betalains are not found in all plants, and they are relatively rare compared to other pigments. Their biosynthesis and regulation in plants are still not fully understood, and further research is needed to fully understand their potential benefits and uses. This review covers research results and demonstrates the therapeutic potential of Betalains across a range of disorders.

Keywords: Betalain, Anthocyanins, Betaxanthin, Betacyanin

Introduction

Betalains are water-soluble nitrogen-containing pigments, The vibrant colouring of fruits, flowers, roots, and leaves of plants belonging to the order Caryophyllales is caused by betalains, which are hydrophilic pigments.[1] Plants from the majority of the Caryophyllales groups have betalains that accumulate in their flowers, fruits, and occasionally even in their vegetative tissues.[2] The practice of using pigments derived from natural sources has gained prominence in recent years. Fruit yoghurt, ice cream, jams, sauces, soups, and cosmetic care items all use betanin as a colouring additive in the culinary business.[3] Betaxanthins and betacyanins are the two main subgroups of betalains, which range in colour from yellow to red-violet. These pigments are confined to 13 families of the order Caryophyllales and a few higher fungus species (Amanita muscaria, Hygrocybe and Hygrophorus). Alternanthera, Amaranthus, Beta, Chenopodium, Celosia, and Gomphrena are only a few of the many genera in the Amaranthaceae family that contain betalains.[4] The evolutionary mechanisms causing the mutual exclusion of the betalain and anthocyanin pathways in flowering plants must be clarified through molecular investigations. Moreover, betalains were found in certain higher fungi, such as the fly agaric (Amanita muscaria). While the roles of betalains in plant flower and fruit coloration are obvious, it is unclear what they play in fungi.[5]

Betalains also have various Pharmacological effects in the medium of their subgroups. A group of substances known as betacyanins have antioxidant and radical-scavenging properties.[6] They are known to stop oxidative processes, which are a factor in the development of a number of degenerative diseases in humans. Red beet products may offer defence against several oxidative stress-related illnesses because betanin exerts a strong bioavailability.[5] Additionally, Betalains can function as osmotic agents to control plant osmotic pressure and play significant roles in how plants react to challenging environmental situations. The research on the physiological development of Betalains is virtually finished, but it is still difficult because it is unclear how Betalains and anthocyanins evolved.[7]

In this review we are discussing the various prominent sources for betalains, chemistry, biosynthesis of betalain as well as in addition to that Pharmacokinetics and Bioavailability studies, any kind of toxicities and reported pharmacological potential related to the Betalains.

Sources

While unraveling the sources of betalains are following in the various plant, fruits, flowers as well in the various fungi, Red beet roots (Beta vulgaris L.), gritty or leafy amaranth (Amarathus sp.), fruits of the cactus Opuntia sp., Eulychnia sp., and Hylocereus sp., among them the dragon fruits of primarily Hylocereus polyrhizus (Web.) Britton and Rose and related species, are the most well-known culinary sources of Betalains.[8, 9] The colored Swiss chard (B. vulgaris L. ssp. cicla),[10] Celosia argentea L.[11] and Bougainvillea sp.[12] Less frequent sources comprise the tubers of ulluco (Ullucus tuberosus Caldas) [13] and the bloodberries (berries of Rivina humilis

L.).[14] Several species of Amaranthus are consumed fresh or cooked.[15,16] Interestingly, tissues of grain amaranths such as Amaranthus cruentus L., A. coudatus L. and A. hybridus L. comprise more betacyanins than those of A. tricolor L., a vegetable amaranth.[17] Unexpectedly, betalains are also found in fungi belonging to the genus Amanita, including Amanita muscaria (L.) Lam. (fly agaric), Hygrocybe, and Hygrophorus.[18-20] Their function in fungi is unclear. The production of dopaxanthin by the bacteria Gluconacetobacter diazotrophicus has recently been reported as a spontaneous occurrence of a betalain in a bacteria.[21]

Chemistry & Biosynthesis

Betalains are immonium derivatives of betalamic acid [4-(2-oxoethylidene)-1, 2, 3, 4- tetrahydropyridine-2, 6-dicarboxylic acid]. When this structure is combined with amines and/or their derivatives, yellow betaxanthins are produced, however when betalamic acid is combined with cyclo-dopa [cyclo-3-(3, 4-dihydroxyphenylalanine)] or its glucosyl derivatives, violet betacyanins are produced.[22, 23]

Compared to flavonoids and carotenoids, betalains' synthesis processes, as well as the enzymes involved in the pathway, are significantly less well characterized. A quarter of a century ago, the biosynthetic steps were initially postulated. But primarily based on phytochemical data, such as feeding studies. The route can be clarified in terms of both molecular biology and biochemistry thanks to developments in molecular biological techniques. This article reviews recent key developments in the betalain biosynthesis pathway with an emphasis on DOPA 4, 5-dioxygenase (DOD) and cDOPA 5-O-GT (cDOPA5GT).

The biosynthetic pathways are composed of a number of enzyme reaction steps and spontaneous chemical reaction steps. There are 3 major enzymes involved in the biosynthesis of betalains, Tyrosinase and 4, 5-DOPA-extradiol-dioxygenase are two examples of oxidases whose catalysis is dependent on molecular oxygen. The additional enzyme embellishes the betacyanin structural unit by transferring a sugar residue: betanidin-glucosyltransferase. In plants, the transcription level regulates the major enzymes involved in the pathway.[24,25] Tyrosine hydroxylase catalyses the formation of DOPA, followed by the synthesis of betalamic acid by DOPA 4, 5-dioxygenase , the production of cDOPA by plant PPO or DOPA oxidase , the conjugation of betalamic acid and amino acids, amines, or cDOPA, and modifications with sugar molecules Despite the fact that DOPA is a crucial precursor to several secondary metabolites in plants, including tyrosine hydroxylase from P. grandiflora, there have only been a few studies of its partial purification.[1,26] Although there is a correlation between the accumulation of PPO mRNA and the levels of betacyanin in pokeweed tissues, there is no direct proof that PPO actually converts DOPA into cDOPA in vitro.[2]

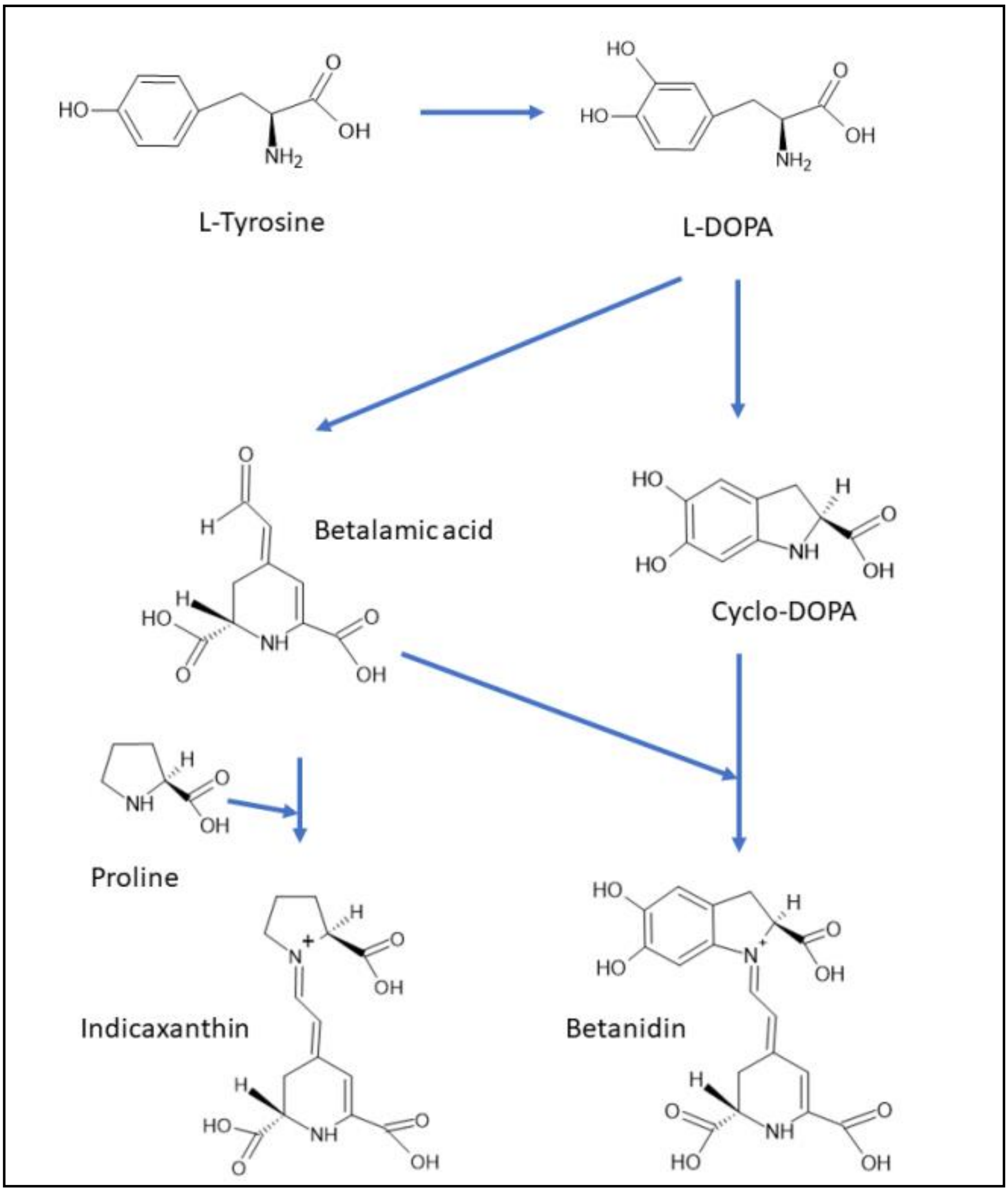

Figure No.1: Biosynthesis Pathway

Pharmacological Evidences

Betalains are the coloring pigment, in the plant which posses various pharmacological activity while in the it posses potent antioxidant activity,[28] anti-inflammatory,[29] along with analgesic effect also seen in the treatment with betalains.[29] Many of the authors also reported the betalains having activity in the cognitive impairment as well it is a well described neuroprotective effect in the animal model.[6] Betalains metabolites was confirmed their activity as radioprotective [30, 31] against multiple radiation in the experimental animals. Also, betalains having an antidiabetic activity.[32] The finding that betalains are the origins of nitrates has sparked recent interest in them. For the prevention or treatment of cardiovascular failure, [33] this may have significant ramifications. With the help of cell line studies antineoplastic[34] and anti-glaucomic.[35] effect betalain was confirmed. Overall, the pharmacological actions of betalains make them a promising candidate for the development of natural medicines and therapies. However, further research is needed to fully understand their potential benefits and to develop effective treatments based on Betalain.

Table No. 1: Pharmacological evidences of Betalains

Sr. No.	Summary	Study Design	Reference
1.	**Anti-inflammatory Effect:** In summary, As a result of its suppression of carrageenan-induced leukocyte edema and leukocyte recruitment, the present investigation demonstrated that the betalain-rich dye of Beta vulgaris elicited substantial anti-inflammatory effects. The mechanism behind these anti-inflammatory actions relies on the suppression of superoxide anion and pro-inflammatory cytokines (TNF-a and In addition to enhanced anti-inflammatory (IL-10) cytokine release, IL-1b production is also involved. Therefore, in addition to its application as a food colouring, this betalain-rich dye of Beta vulgaris generated from food has a therapeutic potential for the treatment of inflammation-related disorders. Therefore, it justifies additional pre-clinical and perhaps clinical research.	Betalain (30-300 mg/kg *i.p.* & 100 mg/kg *s.c.)* Treatment was given in different doses via different route of administration. Male Swiss Mice (20-25 g)	(36)
2.	**Analgesic Effect:** In conclusion, the current study showed that betalain-enriched Beta vulgaris dye exhibits strong analgesic efficacy by preventing overt pain-like behaviour induced by acetic acid, PBQ, formalin, and CFA. Betalains also decreased mechanical hyperalgesia induced by carrageenin and CFA. The reduction in	Betalains [10–1000 mg/kg; intraperitoneal & subcutaneous route (*i.p.*) and (*s.c.)* Treatment was given in different doses via different route of administration.	(37)

	NF-B activation, cytokine release, and oxidative stress is likely the cause of all these effects. This shows that betalains may have broader therapeutic uses because these targets are implicated not just in inflammatory pain but also in other inflammatory events such oedema development and leucocyte recruitment. The current research shows that betalains are interesting substances for the creation of new analgesic treatments.	Male Swiss & C57BL/6 mice (25–30 g)	
3.	**Antioxidant effect:** In the study described here, the author discovered that betalain extracts from hairy root cultures of the red beet B. vulgaris cv. Detroit Dark Red also had higher antioxidant activity than extracts obtained from mature beetroots: six-fold higher 2,2-dyphenyl-1-picrylhydrazyl radical scavenging ability (90.7% inhibition, EC50= 0.11 mg, vs 14.2% inhibition, EC50=0.70 mg), and 3.28 High amounts of total phenolic concurrent compounds (more than 20 times higher) were found in the hairy root extracts, which may have synergistic effects with betalains.	Hairy root culture obtained from beta vulgaris was used for standardization of the antioxidant assay.	(28)
4.	**Radio protective and Antioxidant Effect:** The author discovered that administering red beet betalains greatly reduced the hepatic GSH depletion brought on by -ray irradiation and increased GSHPx activity. MDA is produced when free radicals damage the phospholipids in cell membranes and circulate in the blood. Red beet betalains were found to considerably lower the MDA level, according to the current study. The study by the authors demonstrates that red beet betalains represent a promising radioprotective agent with a significant antioxidant activity.	In this study author administered from (5-80 mg/kg) of betalains as a treatment Male ICR mice (18-22 g)	(30)
5.	**Radio protective:** Author observes in conclusion, beetroot	Beetroot extract 400 mg/kg *p.o.* was given	(31)

	betalains appears to have protective benefits against ionizing radiation when administered simultaneously with c-ray irradiation. These effects include a large reduction in DNA damage, a considerable increase in proliferation, and stimulation of hematopoietic progenitor cells. Although further research is required to determine which beetroot components have radioprotective properties, beetroot is a possibility for a nontoxic radioprotective agent and its aqueous extract has the radio-protective effect.	as treatment C57BL/6 mice were used	
6.	**Cardioprotective Effect:** Throughout this study, the authors present evidence that the usage of betalains can successfully shield cardiomyocytes from oxidative and inflammatory-induced cell damage, preventing tissue remodeling and cardiac fibrosis in the process. The outcomes presented here are based on a thorough examination of the molecular level tests performed to comprehend the interaction between the protein and miRNA in illuminating the potential cardioprotective pathway. Overall, the work suggests a prospective molecule for further research into the well-established molecular cause of heart failure.	betalain (100 mg/kg, *p.o.*) was given in the treatment group Wistar male rats weighing 130 g were used	(33)
7.	**Neuroprotective Effect:** Authors discovered that Betalain prevents AlCl3-induced learning deficits, tissue damage, and cholinergic dysfunction by preventing the production of oxidative free radicals, which may be a result of Betalains strong antioxidant effect. These findings imply that Betalain might be a promising therapy option for neurodegenerative diseases. Before the clinical trials, more research is required to confirm the anti-Alzheimer activity of Betalain against various AD models.	The rats were supplemented with low and high betalain doses (10 mg/kg and 20 mg/kg *p.o.*) for four weeks Sprague Dawley (SD) rats (7–9 weeks, 170–190 g) were used.	(6)

8.	**Antineoplastic Effect:** In this study authors describes about Potential chemotherapeutic effect of betalain against human non-small cell lung cancer through PI3K/Akt/mTOR signaling pathway	Human non-small cell A549 lung cancer cell line and balb/c mice were used	(34)
9.	**Anti-Glaucoma Effect:** As with the other inflammatory cytokines of CXCR4, IL-17, IL-1, and TNF-, which are known to be raised in PC-12-glaucoma model cells without betalain therapy, a decrease in IL-6 might aid in lowering the effects of glaucoma. While the trend is reversed when betalain is used by the cells to try and recover from the hydrostatic pressure effect of glaucoma. Therefore, the results of this study indicate that the medication candidate betalain is a promising candidate to move on to the next stage of research in the glaucoma animal models to be used.	PC12 cell line, the neuronal cells for the experimental model for ocular diseases were used	(35)
10.	**Hepatoprotective Effect:** Beta vulgaris root ethanolic extract shown considerable dose-dependent hepatoprotective efficacy against carbon tetrachloride (CCl4)-induced hepatotoxicity in rats when administered orally at different dosages. Serum indicators including cholesterol, triglycerides, alanine amino transferase, and alkaline phosphatase were used to assess hepatotoxicity and its prophylaxis.	Beta-Vulgaris extract 1000, 2000, 4000 mg/kg *p.o.* treatment was given. Wistar rats of either sex, weighing (100–150 g) were used.	(38)

Clinical Evidences

There is a growing body of clinical evidence that suggests that betalains, the pigments found in beets, may have several health benefits. Some of the reported clinical evidences of betalains (Table No. 2) including anti-inflammatory, protective role in cardiovascular and liver disorders.

While these clinical evidences are promising, further research is needed to fully understand the potential health benefits of betalains and to determine the optimal dosages and formulations for different health conditions. It is also important to note that consuming beets or beetroot extracts containing betalains should not be used as a substitute for medical treatment and that anyone with underlying health conditions should consult with a healthcare provider before making any dietary changes or taking any supplements.

Table No.2: Clinical Evidences

Sr.No.	Summary	Study Design	Reference
1.	**Anti-inflammatory effects**: Betalains have been shown to have anti-inflammatory effects in several clinical studies. In a clinical trial, patients with osteoarthritis who were given a beetroot extract containing betalains experienced a significant reduction in pain and inflammation compared to the placebo group.	A double blind, placebo-controlled pilot clinical study	(39)
2.	**Cardiovascular health:** Several clinical studies have suggested that betalains may have a beneficial effect on cardiovascular health. In a clinical trial, participants who consumed a beetroot juice supplement containing betalains for six weeks experienced a significant reduction in blood pressure and an improvement in endothelial function, a key marker of cardiovascular health.	A double blind, placebo-controlled pilot clinical study	(40)
3.	**Hepatoprotective Effect:** Some clinical studies suggest that betalains may have a protective effect on liver health. . In a clinical trial, patients with non-alcoholic fatty liver disease who were given a beetroot juice supplement containing betalains for 12 weeks experienced a significant reduction in liver enzyme levels, a marker of liver damage.	A double blind, placebo-controlled pilot clinical study	(41)

Bioavailability

The bioavailability of betalains, the pigments found in beets, can vary depending on the source and method of consumption. Bioavailability refers to the amount of a substance that is absorbed by the body and is available for use. Several factors can affect the bioavailability of betalains, including:

1. Food matrix: Betalains are often found in the cell sap of plant tissues, where they are bound to other molecules. The food matrix in which betalains are consumed can affect their bioavailability. For example, consuming betalains in the form of a juice may increase their bioavailability compared to consuming them in the form of whole beets or other foods.

2. Processing: The processing of beets and beet products can affect the bioavailability of betalains. For example, cooking or processing beets can reduce the bioavailability of betalains by breaking down the cell walls and releasing enzymes that can degrade the pigments. Conversely, some processing methods, such as fermentation, may increase the bioavailability of betalains by breaking down the cell walls and releasing the pigments.

3. Gut microbiota: The composition of the gut microbiota can affect the bioavailability of betalains. Some studies suggest that the gut microbiota can metabolize betalains, which can affect their absorption and bioavailability.

Overall, the bioavailability of betalains can vary widely depending on the source and method of consumption. While more research is needed to fully understand the factors that affect the bioavailability of betalains, consuming beets or beet products in the form of a juice or a supplement may be a more effective way to increase their bioavailability compared to consuming whole beets or other foods.[42, 43]

Table No.3: Some evidences of bioavailability

Sr.no.	Description	Reference
1.	The peak plasma concentration of indicaxanthin was determined to be 0.22 M following a single oral dosage of 2 mol indicaxanthin/kg body weight to rats, and the terminal elimination half-life (T1/2) was 1.15 h. Indicaxanthin had a 21% bioavailability in rat urine.	(44)
2.	In a rat experiment, administered betanin was primarily digested in the small intestine (35%), colon (60%) and stomach wall (74%). Around 2.7% of unmetabolized betanin was eliminated in the urine and faeces, while the liver only metabolized a minor portion of betanin.	(45)
3.	When fermented red beet juice was given intragastrically to rats and was absorbed from the stomach, betacyanins	(46)

	suffered extensive degradation. 19 betacyanins, including 8 original chemicals and 11 metabolites, were found in the animals' bodily fluids. Betacyanin concentration peaked in the portal vein 15 and 30 seconds after the extract was administered (0.86 and 12.35 M for 5 mg and 20 mg betacyanins, respectively). Betacyanin excretion in urine peaked after 15 and 30 seconds (0.14 and 3.34 mol/h following the administration of 5 and 20 mg betacyanins, respectively).	
4.	In a Randomized Controlled Trial in Humans, After consuming either 300 g of whole beetroot or 250 mL of beetroot juice, both of which contained roughly 194 mg of betanin, another group was unable to identify betanin in blood plasma at any point in time.	(47)
5.	When given 300 mL of red beet juice containing 120 mg of betanin, volunteers on a polyphenol-free diet excreted 0.5-0.9% of the substance in their urine. Up to 12 hours after eating, the colour was still detectable in the urine, but no byproducts of betalain metabolism were discovered. The majority of betanin was still present in the GI tract, where it may be acting as an antioxidant.	(48)
6.	Following the ingestion of 500 g of cactus pear fruit pulp containing 28 mg of indicaxanthin and 16 mg of betanin by volunteers, both substances were detected in their blood plasma after 60 minutes, reached their peak levels after 3 hours (0.20 M for betanin), and vanished from plasma after 12 hours. Both substances were eliminated with half-lives of 2.36 hours for indicaxanthin and 0.94 hours for betanin, according to first-order kinetics. 76% of the indicaxanthin and 3.7% of the ingested betanin were eliminated in urine over the course of 12 hours.	(49)

Future Aspects

Betalains are pigments that contain nitrogen and have been shown to have a number of notable pharmacological effects in experimental animal models. As a result of betalain's in-vivo and in-vitro pharmacology. In order to enhance their activity from a clinical perspective as well. Betalains have shown potential as phytopharmaceuticals, which are plant-based compounds with medicinal properties. Their unique chemical structure and properties make them an attractive candidate for the development of natural medicines and therapies. While further research is needed to fully understand the potential of betalains as phytopharmaceuticals, they have shown promising results in preclinical studies and have a low risk of toxicity. However, it is important to consult with a healthcare professional before using betalain supplements or phytopharmaceuticals products, especially if you are pregnant or have a medical condition.

Conclusion

When possible, betalains are a suitable choice to replace synthetic colourants since they are present in a wide variety of plants, are very simple to obtain in more-or-less pure forms, and are more stable than anthocyans and anthocyanidins at near-neutral pH. The latter is frequently used as a compromise between aesthetic effects and potential health risks, whilst betalain may bring additional benefits to health beyond colour. Also, they have uses outside the food sector. Although data on the effects of fruits or juices may be skewed by the presence of other, non-betalain components present in these materials, further research on pure molecules is required to fully understand their health-promoting effects. Betalains also have creative uses outside the food business. In adding that betalains having a well-established activity in the various animal that could help us for in future clinical significances.

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