Original Article

A General Study Of Stability Enhancement Factors, Formulations, And Pharmacological Application Of Glycosidic Dye Betalain

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Abstract

Fresh vegetables greatly minimize the risk of toxicity and other degenerative and chronic diseases. The vegetable beetroot possesses anti-inflammatory, anti-cancer, anti-microbial, and coloring properties in addition to its natural antioxidant capacity. They are water-soluble nitrogenous pigments. Betalains are frequently employed as a natural red food colorant and for their potential as antioxidants. The pigments that give flowers and fruits their colors are those that are water-soluble. They are composed of yellow betaxanthins and red-violet betacyanin. Balsamic acid is an ingredient in all betalains. The type of balsamic acid substitution determines the class of betalains. Cyclo-3,4-dihydroxyphenylalanine (cyclo-DOPA) residues are present in the betacyanins, which range in color from red to violet. while the betaxanthins have a variety of amine or amino acid residues (yellow to orange). The most common betacyanin is betanin, a glucoside of betanidin that is present in red beets and also goes by the name "beetroot red" (Beta vulgaris). Talain has a higher bioavailability than most flavonoids, which is its main advantage as a dietary antioxidant. Due to its low cost and non-toxicity, it is a glycosidic natural color used in the food and pharmaceutical industries. This contribution's major goal was to investigate the most prevalent betalain's fundamental source, isolation methods, and therapeutic and pharmacological applications.

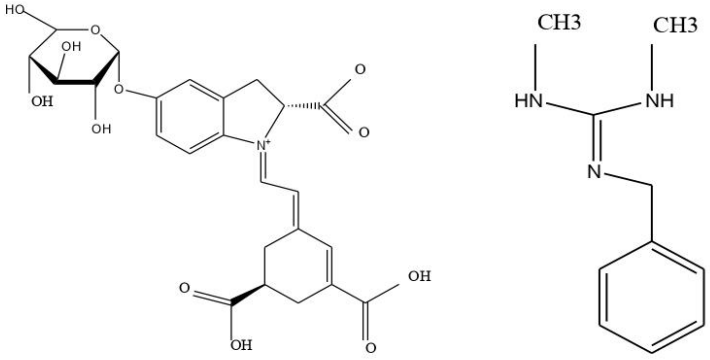
Keywords: Betanin, Betalain, Beetroot, Glycosidic dye, Anti-oxidant

INTRODUCTION

Natural ingredients have been chosen because of their advantageous qualities, cost-effectiveness, and low toxicity. Several studies have been done in this field, including those on antioxidants, anti-diabetics, anti-cancer, and anti-microbial. Betanin (also known as betalain) was chosen for my research due to its beneficial properties, ability to be extracted from widely available plant sources, and availability in numerous nations throughout the world [1]. Beetroot (Figure 1) (Beta vulgaris L., belongs to the family Chenopodiaceae) and contains the active component betanin. It is a nitrogen-containing red glycosidic water-soluble dye that is employed as a coloring agent and is pH-sensitive. Mainly it comprises red-violet betacyanins and yellow betaxanthins. Betanin (75–95%) is the major

constituent of red pigment and vulgaxanthin I, the principal pigment of the yellow betaxanthin group. Another yellow pigment, betalamic acid, derived directly from the cleavage of betanin is probably the key intermediate in all betalains. It hydrolyzes into the sugars glucose and betanidin (aglycon part) (Figure 2) [2]. The primary phytochemical representative, 5-O-D-glucoside, a water-soluble nitrogenated heterocyclic bioactive molecule, is what gives reddish-violet plants their color [3]. The only betalain that has been approved for use in food is betanin (CI, E-number E162, Natural Red 33 betanidin 5-Ob-glucoside), which is almost entirely derived from red beet crops [4-7]. According to Kapadia et al. 2003 and Fechner et al., 2010, in-vivo experiments have shown that very low concentrations of dietary pigments inhibit the formation of tumours in mice [7]. According to other descriptions, betanin is a bioactive substance that can inhibit the low-density lipoprotein (LDL) and peroxidation of lipid membranes, modulate the production of reactive oxygen species (ROS) and gene expression to lessen the release of inflammatory cytokines, and boost the activity of antioxidant enzymes [8]. It has natural antioxidant potential which may have positive effects on humans [8]. Phytochemical compounds responsible for the antioxidant capacity most likely the phenolic acids, anthocyanin, and other flavonoid compounds like betacyanin. The potential beneficial effects of the high antioxidant capacity and protection of cells from free radical attack seem clear [2].

Figure 1. Natural Beetroot powder



Betanin with sugar components Betanidine

Figure 2. Structure of Betanin and Betanidine

Wu et al., 2006 and Sreekanth et al., 2007 said that betanin is effective in cancer therapy. Different cell lines have demonstrated the potential of betalains in the chemoprevention of lung and skin cancer [2]. According to a study, complex formation by selenium (antioxidant metals in nature), which stabilizes betalains, may increase the bioavailability of betalains. This review article reveals the therapeutic potential and pharmacological applications of betalain as well as the literature's findings that have been reviewed and highlighted. It is a promising substitute for manufacturing, utilization, and further therapy.

Source of Betalain

A suitable option for replacement as an active component with coloring qualities in formulations is betalain, which is found in many plants (partially pure form) in an adequate amount **(Table 1)**. Anthocyanins and anthocyanidins are more stable compared to betalain (at neutral pH).

Table 1. Common Betanin source and its pigment

Sl No	Betalain source	Bitalain pigment	Reference
1.	Red beet (Beta vulgaris)	Yellow betaxanthines pigments and Purple betacyanins. Isobetanin (isobetanidin-O-ß-glucoside), isobetanin	2
2.	Opuntia species	The yellow betaxanthins, red to red-violet betacyanins indicaxanthin isobetanin	9
3.	Hylocereus sp	The 5-o-betanidin (20 -O-b-D-apiofuranosyl) b-D-glucopyranoside (40 -O-malonyl), Betanidin 5-O, (-b-D-glucopyranoside-b-D glucopyranoside) and Betanidin 5-O-[(500-O-E-sinapoyl)-20 -O-b-D-apiofuranosyl].	10
4.	Hylocereus polyrhizus (Web.) Britton	Deep-purple seven major betacyanins are Betanidin-5-O-b-glucoside (Betanin), Betanidin-5-O-b-sophoroside (Bougainville in r-I), Iso-betanidin-5-O-(60 -O-3-hydroxy-3-methyl-glutaryl)-b-glucoside, Isobetanidin-5-O-b-glucoside (Isobetanin), Betanidin-5-O-(60 -O-malonyl)-b-glucoside (Phyllocactin), Betanidin-5-O-(60 -O-3-hydroxy-3-methyl-glutaryl)-b-glucoside, Betanidin-5-O-(60 -O-3-hydroxy-butyryl)-b-glucoside, Unknown betacyanin, Isobetanidin-5-O-(60-O-malonyl)-b-glucoside (Isophyllocactin)	11
5.	Celosia argentea L.	Yellow ammonium conjugates betalamic acid with, dopamine, yellow 3-methoxytyramine and (S)-tryptophan	12
6.	Bougainvillea sp	Betaxanthins are those betalain pigments that appear yellow to orange and Betacyanins including reddish to violet betalain pigments and Betacyanins	13
7.	Phytolacca americana L.	yellow-orange betaxanthins and Red-violet betacyanins	14
8.	Gluconacetobacter diazotrophicus	The violet betacyanins and yellow betaxanthins	15

Factors that affect the stability of betalain

The volatility of betalains is one of the key issues limiting their use. Several factors, including oxygen atmosphere, pH, temperature, light, heating, and air, affect the stability of betalain. The reversibility of this reaction, which is not seen in the presence of oxygen, is the reason why the kinetics of aerobic degradation of betanin differs from that of the first-order reaction in the absence of oxygen (Figure 3). A nitrogen environment improves betalains'

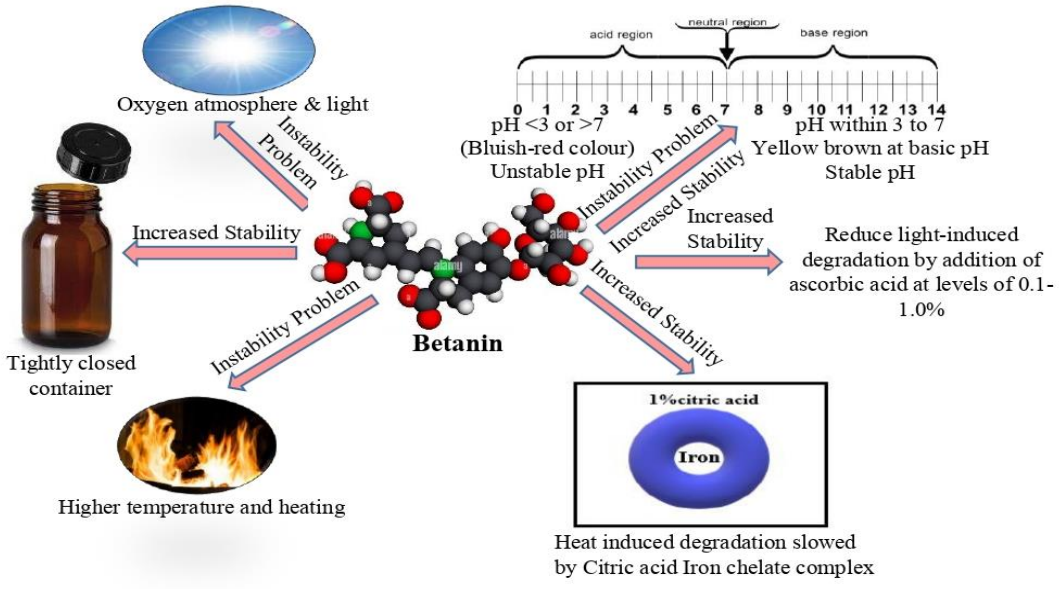


Figure 3. Factors that affects stability and stability enhancement process of Betanin

stability [16-19]. Low oxygen storage of betalain solutions can stop the pigment from deteriorating [20-21]. Reactive oxygen species (ROS) mediate the breakdown of betacyanins in aerobic environments [3]. Today's storage methods include improved stability, as well as processing and extraction methods, and they are all kept in firmly covered containers out of the sun and heat [22]. Betalains are heat-sensitive and start to break down at temperatures higher than 50℃. High temperatures cause betacyanins to degrade, producing yellow by-products such as freshly produced betaxanthins, balsamic acid, and neobetacyanins [23]. Boiling betanin-containing material causes the glycoside to be eliminated along with an increase in the proportion contribution of dehydrogenated and decarboxylated betanin derivatives [3]. Reduce heat-induced degradation by the addition of 1% citric acid, which also serves as a preservative of colour stability by chelating metal ions, among which iron is particularly prone to decompose the betacyanin. Reduce light-induced degradation by the addition of ascorbic acid at levels of 0.1-1.0%. According to reports, betanin has a fairly wide pH range of stability (bluish-red colour) between pH 3 and 7, only changing to yellow-brown at basic pH. When kept at 4 °C, betanin remained stable at pH 7 for at least 20 days and more than 275 days. The red color changes to pale brown when heated, exposed to air, or exposed to light [22]. While acidity leads balsamic acid to condensate with the amine group of the substituent residue, alkaline circumstances trigger the hydrolysis of the aldimine bond [24-25]. Under acidic circumstances, C15 isomerization and dehydrogenation were seen. Betanidin breaks down into methylpyridine-2,6-dicarboxylic acid and 5,6-dihydroxyindole-2-carboxylic acid in both alkaline and acidic conditions. Oxygen molecules react with betalains. At last, Stintzing and colleagues reported in 2006 that even greater thermal stability of the pigment was attained by mixing a comparable amount of ascorbic acid (Vitamin C) with the betalain extract generated from the purple pitaya fruit.

Neobetanin, which causes the color to turn yellow, is produced when betanin undergoes dehydrogenation during heating. The colorless cyclo-DOPA-5-O-glycoside and the yellow balsamic acid can also be produced during cleavage. The lowest betanin stability was found in the water/ethanol system, according to a comparison of the thermal degradation of betanin in three model solvent systems (water/glycerol, water/ethylene glycol, and water/ethanol) at temperatures between 60℃ and 86℃. This finding supports the idea that the nucleophilic assault on the aldimine bond 106 represents the first stage of betanin's heat breakdown since

ethanol has a high electron density on the oxygen atom. It has been suggested that esterifying betacyanins with aliphatic acids will increase their stability [3].

Preferred formulation

Since these pigments are unstable to physicochemical factors like high temperature, pH fluctuations, and high water activity, they have not been able to be potentialized in a variety of fields like pharmacology, despite being utilized as colorants in several foods and medicinal preparations. Due to this, numerous stabilization strategies have been reported to stabilize betalains in a variety of encapsulation techniques to draw precise conclusions about how encapsulation affects their stabilization and to suggest new methods and matrices that could facilitate it **(Table 2)** [1].

Table 2. List of preferred formulation

Sl No	Preferred formulation	Observation	Reference
1.	Double emulsion	• Although the stability of a double emulsion for 180 minutes was high, longer-term storage needs more research. The rate of betalain emission is extremely low. • The double emulsion demonstrated excellent encapsulation performance as well as emulsion stability.	26
2.	Microparticle	• Ethyl cellulose (EC), a 20% polymer that is utilized as a microparticle matrix and has a higher level of antioxidant stability than dry beetroot, can maintain the stability of betanin. • Due to a higher concentration of the EC polymer in the organic phase during the synthesis of the microparticles, the particle size and entrapment were larger.	27

- Betanin was more stable in microparticle form than in dry beetroot extract, and EC 20% as a matrix provided the best defense against losing betanin's stability.

The pharmacological activity of Betalain

Because of their various positive effects, dietary betalains may be crucial in preserving human health. The effects of betalains on health are well documented (Figure 4). Betalains are used in a variety of inventive ways outside the food business. Red beetroot and its active constituents, betalains, have been linked to several health advantages, including antioxidant, anti-inflammatory, anticancer, blood pressure, and lipid-lowering, as well as actions that are anti-diabetic and anti-obesity.

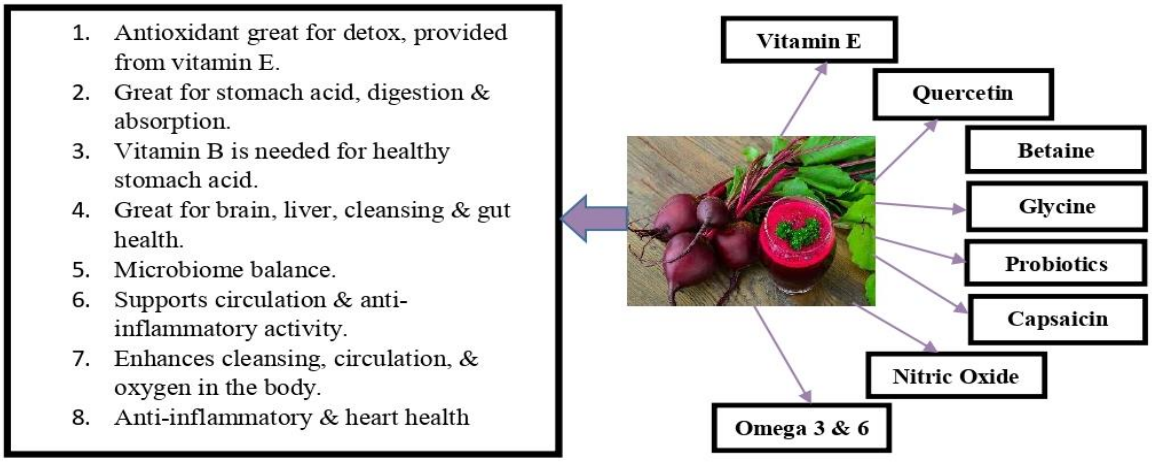


Figure 4. Different pharmacological activity of Betalain

Anti-inflammatory activity

Additionally, it has been represented that betalains significantly reduce the in vitro expression of cyclooxygenase-2, a vital enzyme that transforms arachidonic acid into the chemical mediators of inflammation known as leukotrienes and prostaglandins. The formation of neopterin, a sign of immune system activation, and the breakdown of tryptophan in human peripheral blood mononuclear cells were both inhibited by extracts of Beta vulgaris in a dose-dependent manner. The presence of extracts reduced the cellular response to stimulation, indicating that they include substances with immunosuppressive and anti-inflammatory properties [1]. One of the most effective anti-inflammatory substances is betalains. Beetroot extract was administered to nephrotoxic rats for 28 days in a preclinical trial, which revealed reduced Nuclear Factor-Kappa B (NF-B) DNA binding activity. Another study demonstrates that administering betanin to rats with acute renal injury for 5 days at doses of 25 and 100 mg/kg/bm decreases NF-B DNA binding activity [28].

Cardiovascular Disease (CVD)

Systolic and diastolic blood pressure was observed to be reduced when red beetroot was applied as a juice supplement. Human volunteers who took betalain-rich supplements (50 mg of betacyanins /betalain for two weeks on daily basis) had decreased systolic and diastolic blood pressure. Blood lipid levels were dramatically reduced by red beetroot betalains without any toxicity or negative side effects. Triglyceride concentrations, cholesterol, and LDL cholesterol (LDL-c) levels are CVD risk factors [8].After 30 days of intake, 22 students between the ages of 18 and 45 were tested for their responses to the effects of dietary quinoa on risk factors for CVD (quinoa

includes a significant concentration of betalain 15.2 mg/50 gm dry portion). About 40.7% and 42.2% of the participants, respectively, exhibited hypotension and decreased body weight.

Hepatoprotective effect

Betanin, in particular, and betalain containing red beet extract in general, have been shown to have hepatoprotective effects. However, other factors, including the improvement of liver redox status, induction of the detoxification phase II enzyme quinone reductase, and mitochondrial functions, have also been proposed [1].

Anticancer activity

Opuntia ficus-indica extracts immortalized ovarian and cervical epithelial cells in addition to inhibiting the growth and inducing apoptosis in several ovarian, cervical, and bladder cancer cell lines. Melanoma cell proliferation was inhibited by extracts from the fruit of the cactus Hylocereus polyrhizus in a concentration-dependent manner. Peel extracts had a greater impact than flesh extracts, which was likely due to the peel's increased betalains and flavonoid concentration. Melanoma cell development was likewise severely suppressed by pure betanin.
Treatment with the extract stimulated both intrinsic and extrinsic mechanisms of apoptosis in breast cancer cells. Previous research, especially in human cell lines, such as those from pancreatic, breast, and prostate cancer, has revealed that betalains are prospective agents for promoting chemotherapeutic techniques [1].

Anti-microbial activity

The antiviral, antibacterial, antifungal, and antiprotozoal properties of betalains have been established. Escherichia coli growth was discovered to be inhibited by extracts of Opuntia mature Scheinvar that contained betalain. The growth of Bacillus cereus, Staphylococcus aureus, and Salmonella typhimurium was prevented by beetroot (Beta vulgaris L.) pomace. Gram-negative bacteria growth was also shown to be inhibited by beetroot pomace in a different investigation. The effects of betalains on permeability, the structure, and other features of the cellular membranes, which are obtained from microorganisms may contribute to their antibacterial activity and finally cause cell death. Red beetroot often makes Gram-positive bacteria more sensitive than Gram-negative bacteria [1].

Anti-diabetic Activity

Yanardag et al. found that diabetic rats given Beta vulgaris L. var. cicla (BVSc) extract had low blood sugar levels. Further research revealed that these rats' glycemia was decreased to 40% without resulting in weight loss or hepatic damage. The saponins in the extract are thought to have a hypoglycemic effect because they stop gluconeogenesis and glycogenolysis. Therefore, it is crucial to carefully explore the molecular pathways that have an impact on this hypoglycemic process. Numerous investigations suggested that flavonoids may be responsible for the hypoglycemic effect of the BVSc extract, which is mediated by the suppression of glucose transporters. For instance, the BVc compound quercetin demonstrated antidiabetic benefits by inhibiting the activity of the intestinal glucose transporter GLUT2 [28].

Hepatitis

In a human experiment, a supplement containing raw red beet juice reduced non-HDL-c, LDL-c, and total cholesterol. In mice with AML, betanin treatment decreased LDL levels. In contrast to having greater levels of blood TC, the HDL-c/TC ratio, triglycerides (TAG), and the atherogenic index, rats fed a non-lipid diet produced fewer short-chain fatty acids (SCFAs). On the other hand, red beetroot crisps reduced the production of TC and TAG, raising the possibility of a high total SCFA pool. Additionally, the injection of 3% RBR crackers reduced hepatic TC. These findings suggest that giving rats with dietary dyslipidemia RBR crisps will avoid metabolic changes. However, another rat study found that while RBR consumption reduced the levels of SCFAs, it also led to the build-up of fatty acids long-chain [28].

Cognitive Impairment

The majority of patients who have Alzheimer's disease and Dementia experience circulation of cerebral problems. Nitrate can help with circulatory issues since it is digested and produces nitric oxide (NO) in beets. Magnetic resonance imaging (MRI) of the brain revealed a significant increase in blood flow in regions of the brain associated with cognitive activity in a study of 75-year-old volunteers on a diet including red beet juice. Contradictory findings, however, were found in other studies about the design and study groups chosen. Red beet extract contains a betaine component that has been found to help prevent the buildup of undesirable proteins in the brain, a condition linked to Alzheimer's disease. Betaine is a promising substance for preventing the negative brain processes that contribute to the progression of Alzheimer's disease. A sticky protein or peptide fragment called beta-amyloid builds up in the brain and severs the connection between nerve synapses. When amyloid beta binds to metals like Fe and Cu, the harm gets worse. Metals cause the beta-amyloid protein to accumulate incorrectly, causing masses to form that result in inflammation, oxidation, and ultimately the death of nerve cells. The oxidation of the Cu-bound amyloid beta protein was decreased by up to 90% when betanin was introduced, and the aberrant protein folding was halted. Therefore, it seems that the main mechanism of betaine is the reduction of oxidation, which slows down the accumulation of beta-amyloid protein [28].

TOXICITY OF BETALAINS

The only industrial source of betalains is red beet. The Phytolaccaceae plant R. humilis L., which is high in betalains, might be used as a substitute source for these pigments. Berry juice was given to male rats that were adults (single-dose: 1, 2, and 5 g RBJ/kg BW), growing (repeated-dosing: 2.5 and 5 g RBJ/kg BW for 35 days), and fed as part of their diet for 90 days (0.5, 1%, and 2% RBJ in diet, w/w). Compared to untreated control rats, red beet juice (RBJ) was well tolerated in all three investigations. Additionally, they looked at the hematological, the histology of important organs, and the biochemical evaluations of the liver and serum of the drug-treated rats. These findings suggest that the consumption of berry juice does not affect normal biochemical balance or growth [28].

CLINICAL STUDIES

Non-smoking female volunteers (Six healthy) participated in the pilot study. They received 500 mL of tap water or 500 mL of a commercial RBJ containing 362.7 mg of betalains sequentially as a single oral dosage. Up to 24 hours after the treatment, urine samples were taken at intervals. Botulin equivalents were calculated based on the spectrophotometric determination of renal excretion of betalains. However, Plasma NOx was increased 8 hours and 5 hours after BTJ and BF, respectively. Thus, the author concluded that betanin had a low bioavailability but that red beet juice and fruit could help raise plasma concentrations of nitric oxide [28].

DISCUSSION

Since betalains have numerous significant health benefits for both the food and pharmaceutical industries, they have received much research as vital bioactive chemicals. The majority of the scientific literature that is now available shows that the extraction techniques, phytochemical analysis, and some pharmacological activity testing were effective. In extreme pH changes (beyond the limit), high temperatures, oxygen or air, and light, betalains can instantly break down. Researchers have discovered new and intriguing betalain sources that can be used to meet this demand without compromising quality. Technologies like ultrasonic-assisted extraction and encapsulation using various matrixes have the potential to address some of the shortcomings of the conventional approach. Betanin has a beneficial effect on jejunal as well as lung tissue histological lesions caused due to intestinal IR injury. The intestinal mucosa is protected as part of the system, and this indirectly protects the lung parenchyma. Additionally, pre-treatment with betanin has demonstrated the capacity to lessen inflammation followed by intestinal IR injury. From the discussion above, it is clear that betanin, a naturally occurring betacyanin pigment from red beetroot, has renoprotective activity because it significantly reduces peripheral glucose, enhances insulin secretion, and changes the levels of lipid by-products and renal biomarkers in STZ-NA-induced type 2 diabetes. Beetroot extracts, particularly betanin, have been found to have a protective role against

carcinogenesis and to have a cytotoxic effect on tumor cells by specifically targeting mitochondrial malfunction. In order to combat p53 mutant and temozolamide-resistant glioma cell lines without harming healthy cell mitochondria, betanin and temozolamine have been shown to have a synergistic impact. As a result, this combination may be an improved alternative.

CONCLUSION AND FUTURE SCOPE

Despite betanin having various stability problems due to various conditions, there is antioxidant power to prevent premature aging of the skin and it is easily available, natural, non-toxic, and biodegradable that's why betanin is selected. The current study concluded that the formulation of betalain pigments was prepared by the double emulsion method followed by a high encapsulation process. The stability of a control double emulsion for 180 min was high and the release of betalain was very low. The time of storage, stability, and target mechanism should be investigated properly. Furthermore, clinical and preclinical studies must be done and in-depth investigations are needed for the study of all the bioactive phytoconstituent and their biomolecular pathway in the cellular medium of beetroot. In the next paper, our main aim is to prepare a novel formulation for enhancing stability that protects the active ingredients from factors that cause damage, such as changes in humidity, temperature, microorganisms, and oxygen. However, there hasn't been much research done on creating formulations from betanin and studying them in vivo. We create a stable, effective formulation including betanin for further research, and an animal study will be used to demonstrate the formulation's effectiveness.

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ETHICAL ISSUES

It is a review article. No ethical issues are associated

CONFLICT OF INTEREST

Not applicable.

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