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SHORT REVIEW

An Updated Comprehensive Review on the Phytochemical Properties and Nutritional Applications of *Synsepalum dulcificum*

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Abstract

Synsepalum dulcificum (miracle fruit) is a tropical plant valued for its biological, phytochemical, pharmacological, and ethno medical significance. The fruit is unique for containing miraculin, a glycoprotein that modifies sour taste into sweetness. Growing scientific interest highlights its potential in pharmaceutical and nutraceutical development. This review aims to summarize the phytochemical composition, pharmacological properties, ethno medicinal applications, and therapeutic potential of *S. dulcificum*, while identifying gaps requiring further research. A comprehensive literature search was performed using electronic databases to identify studies on the bioactive compounds, pharmacological activities, and traditional uses of *S. dulcificum*. Both experimental and ethno medical evidence were analysed. *S. dulcificum* contains flavonoids, alkaloids, terpenoids, and phenolic compounds contributing to its diverse pharmacological actions. Miraculin remains the most significant constituent for its taste-modifying effects. Pharmacological investigations reveal antioxidant, anti-diabetic, anti-inflammatory, antimicrobial, and hepatoprotective activities. Antioxidant effects are linked to high phenolic and flavonoid content, which reduce oxidative stress. Anti-diabetic potential is supported by modulation of blood glucose levels, while anti-inflammatory and antimicrobial activities suggest utility in managing infections and inflammatory conditions. Ethno medicinally, *S. dulcificum* has been traditionally used in African medicine for treating diabetes, hypertension, gastrointestinal disorders, and infectious diseases. In modern contexts, it has been employed to improve taste perception in chemotherapy patients experiencing dysgeusia. *S. dulcificum* represents a promising plant with multifaceted pharmacological and ethno medicinal applications. Despite its potential, clinical validation of efficacy, safety and mechanisms is still limited. Further high-quality studies are required to establish its role in evidence-based medicine and expand its application in pharmaceutical and nutraceutical industries.

Major Findings: *Synsepalum dulcificum* is rich in flavonoids, phenolics, alkaloids, and the glycoprotein miraculin, which confer antioxidant, anti-diabetic, anti-inflammatory, and antimicrobial effects. Its ethno medicinal and nutritional applications highlight potential use in managing metabolic disorders and enhancing taste perception, warranting further clinical validation.

Keywords: Bioactive Compounds, Miraculin, *S. dulcificum*, Taste Perception

1. Introduction

Synsepalum dulcificum, commonly known as the "miracle berry" or "miracle fruit," is an evergreen shrub native to the dry lowlands of West Africa. Traditionally consumed by indigenous populations in Africa and Asia, the plant has attracted scientific attention due to its unique taste-modifying glycoprotein, miraculin, and its diverse phytochemical and pharmacological properties. In recognition of its novelty, the European

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Food Safety Authority (EFSA) has classified miracle berries as a novel food under regulation (EU) 2015/2283[1].

Nutritionally, the fruit provides vitamin C, flavonoids, amino acids (such as leucine), and essential minerals, making it both palatable and functional. Its hallmark feature is the ability to modify sour taste perception into sweetness through miraculin, which is active only under acidic conditions. Unlike conventional sweeteners, miraculin itself is not intrinsically sweet but binds to the T1R2/T1R3 sweet taste receptor on the oral mucosa, eliciting sweetness in the presence of acids. This phenomenon has spurred interest in its applications in food and nutrition, particularly in improving dietary compliance among cancer patients with taste alterations during chemotherapy[2,3].

Beyond its sensory effects, *S. dulcificum* has been investigated for a range of biological activities. Crude extracts are reported to possess antioxidant, anti-inflammatory, antimicrobial, and anti-diabetic effects in preclinical models[4,5]. Emerging evidence also suggests potential anti-proliferative effects *in vitro*. These findings position the plant as a candidate for both nutraceutical and pharmaceutical applications. However, most data are limited to *in vitro* and animal studies, with a scarcity of well-designed human clinical trials. Moreover, the pharmacokinetics, toxicity profile, and drug-interaction potential of miraculin remain poorly defined, underscoring the need for further research.

Given the growing global interest in plant-based therapeutics and functional foods, this review provides an updated synthesis of the phytochemical composition, pharmacological activities, nutritional applications, and therapeutic potential of *S. dulcificum*. Particular emphasis is placed on differentiating the effects attributable to miraculin from those of crude extracts and other phytochemicals, thereby clarifying its role in modern medicine and nutrition science.

2. Geographical Distribution of *S. dulcificum*

Synsepalum dulcificum is a shrub of the hot tropical lands of parts of Africa which was later distributed to other countries. It is cultivated in large numbers in Japan and Taiwan apart from other parts of America like Jamaica, Florida, Hawaii and other parts of the southern United States of America. It grows well in warm areas with an optimal climate of about 30 and 40° and in slightly acidic soil (pH 4.5 - 5.8). The vegetative phase is the longest phase where there is minimal growth. It enters the reproductive phase after a total of 3-4 years after which fruits are produced. During this phase, the plant grows rapidly and can reach a height of fifteen feet after its complete maturation. The major growth season is from May to September and the berries can be yielded throughout the year. The plant reaches around 15 feet in height after its maturation[6].

3. Botanical Description

Synsepalum dulcificum is a member of the *Sapotaceae* family which includes a total of 40 genera under it. There are a total of 164 scientific names of plants under the genus *Synsepalum* which has its origins from Africa. There are around 30 species under this genus. S. *dulcificum* is one of the eight useful species which are popularly utilized in traditional African folk medicinal practices. The leaves of the shrub are symmetrical, small and have a pointed apex. They are lanceolate and measure 4 to 7.5 cm in length and 3 to 4 cm in width with a length/width ratio of 2:1. There is the presence of a petiole around which the leaves occur in small clusters.

The flowers given by the plant are cream in colour while budding and on maturing turn dark red to brownish. After around 70-74 days following the production of flowers, fruits are given out. Each berry is ellipsoidal and measures 2 cm in length and 1 cm in width and is produced multiple times a year. The berries are initially green which turns into a red colour upon maturing. Some authors have documented the occurrence of yellow fruits in certain varieties of miracle berry plants. The fruits have a central seed that is embedded in white pulp and this part tastes like cherries. The pulp does not contain calories and is the only part of the plant that contains miraculin which is the major glycoprotein for which the plant is cultivated. Each miracle berry weighs around 1.39g with a range of 0.13 to 2.96 g /fruit[6,7]. Miracle berries can be propagated by vegetative methods or by micro-propagation. Propagation through cuttings does not stimulate healthy roots however; micro-propagation

has been shown to proliferate shoots and roots. Specialized mediums like Murashing-skoog with other supporting chemicals help in the easy reproduction of seeds. Seed reproduction is the best technique that preserves genetic variation and gives maximum germination. Studies have shown that miracle berries can give shoot and root propagation at an optimal temperature of around 23°[8].

4. Chemical Composition and Bioactive Compounds of *S. dulcificum*

Synsepalum dulcificum widely known as the Miracle Berry, is globally recognized for its unique taste-altering properties. This effect is due to the presence of a glycoprotein called 'miraculin' found in the fruit's pulp. Miraculin binds to taste receptors of the tongue, making sour foods taste sweet, with the effect lasting up to 60 minutes before neutralization by saliva. Beyond taste modification, miraculin offers potential health benefits, including obesity management and improved insulin sensitivity. It is utilized in the food and beverage industry to enhance palatability, particularly for diabetic individuals, by increasing sweetness without additional calories. Miracle fruit is valued for its flavour, colour, and antioxidant properties. Its berries, leaves, and roots contain carbohydrates, fibre, volatile oils, tannins, alkaloids, cardiac glycosides, polyphenols, flavonoids, resins and minerals. Among the bioactive compounds identified, pentacyclic triterpenes specifically lupenyl acetate and β-amyrin acetate are particularly prominent in seed extracts. These C30 isoprenoids are present in all plant parts. Their quantification based on commercial standards reveals lupenyl acetate to be 25-31% of the total extract and β-Amyrin acetate to be 12-16% of the total extract. The fruit is rich in vitamins A, C, D, E, and K, and essential amino acids (lysine, leucine, isoleucine, phenylalanine, threonine, histidine, valine, tryptophan) and nonessential amino acids like glycine, proline, tyrosine, glutamic acid *etc*. Its deep red colour results from anthocyanins, known for their anticancer potential. Additionally, the fruit contains antioxidant phytochemicals such as quercetin, myricetin, kaempferol, gallic acid, ferulic acid, syringic acid, cyanidin galactoside, α-tocotrienol, terpenoids, phenolic compounds, lutein *etc*[9].

4.1 Compounds Identified in Various Plant Parts

4.1.1 Stem

Methanol extracts of the stem have identified 13 compounds like Dihydro-feruloyl-5-methoxytyramine, Syringaresinol, Vanillic acid and N-Feruloyl tyramine. Some, such as epi-syringaresinol, exhibit anti-ageing and antioxidant properties, while others inhibit tyrosinase activity, making them potential treatments for hyper pigmentation. β-Sitosterol and stigmasterol also possess anti-inflammatory and immune modulating effects as summarised in Table 1.

4.1.2 Leaves

The leaves contain anthocyanins like cyanidin-3-monoglucoside, delphinidin-3-monoarabinoside, cyanidin-3-monoarabinoside, and delphinidin-3-monogalactoside. Chromatographic analysis of the leaves identified eight compounds, including β-Sitosterol, stigmasterol, lupeol, lupenone, α-Tocopheryl, and quinone. Triterpenes such as lupeol possess anti-inflammatory properties. Further biochemical studies revealed the presence of bioactive flavonoids such as quercetin, kaempferol, catechin, and polyphenols.

4.1.3 Roots

The roots contain phenolic compounds like p-hydroxybenzoic acid, vanillic acid, syringic acid *etc*.

4.1.4 Fruits

The fruit is particularly notable for miraculin, a taste-modifying glycoprotein used in pharmaceuticals, along with various flavonoids and anthocyanins responsible for its red pigment. Amino acid profiles of the berry pulp include essential amino acids like isoleucine, phenylalanine, threonine, histidine, methionine, valine, tryptophan and nonessential amino acids like proline, serine, tyrosine, and glutamic acid. Vitamin content includes vitamin A (2.54 ± 0.27 mg/100 g), vitamin C (1.33 ± 0.24 mg/100 g), vitamin E (0.78 ± 0.05 mg/100 g)[10]. The various parts of the plant are summarised and illustrated in Table 2.

4.2 Proximate Composition

The physicochemical properties of the seed extract include moisture content 38.08%, total carbohydrates

29.08%, crude fibre 0.66% and ash 1.43%. Proximate analysis of leaf and fruit extracts revealed carbohydrates at 40.38% in (leaves) and 17.44% in (fruit), crude fibre 17.58% in (leaves) and 3.63% in (fruit), crude protein 8.42% in (leaves) and 10.46% in (fruit), crude fat 1.97% in (leaves) and 2.32% in (fruit). Other components like ash are present around 2.87% in (leaves) and 3.95% in (fruit) and lastly, the moisture content is 28.78% in (leaves) and 62.40% in (fruit). Mineral and proximate composition studies have analysed the mineral composition of different plant parts leaves having calcium, chromium, iron, zinc, and copper. Roots have calcium, chromium, zinc, iron, and copper. Seeds have a majority of sodium, magnesium, iron, zinc, copper, manganese, nickel, and cadmium.

Various bioactive compounds have been identified from different parts of *S. dulcificum*, including alkaloids, lignans, phenolic acids, glycoproteins, phytosterols, triterpenes, and flavonoid pigments. These phytochemicals have broad applications in food, pharmaceuticals, and cosmetics. Recent research has identified 17 novel compounds, including (7S, 8R)-dihydrodehydrodiconiferyl alcohol and quercetin-3-O-glucoside, with strong antioxidant properties. Preliminary phytochemical analysis confirms the presence of saponins, alkaloids, glycosides, phenols, resins, terpenoids, steroids, and cyanogenic glycosides[11].

5. Mechanism of Taste-modifying Action of Miraculin

Various researchers have assessed the phytochemical properties of miracle berries and have stated that the taste-modifying function of this unique plant is due to 'miraculin'. It is a 44-kilodalton glycoprotein identified in the pulp of the fruits. It is a homodimer of glycosylated polypeptide glycoproteins with a total of 191 amino acids and has a molecular weight between 24,000 to 45,000 Daltons in monomeric form. Two researchers namely Kurihara and Beidler isolated miraculin in 1968 and another group of researchers namely Theerasilp *et al.* studied the chemical structure of miraculin in 1989. Miraculin is pH resistant and naturally does not have any sweet taste. Once it is activated to an acidic pH of less than 6.5, it changes the taste from sour to sweet and this sweetness is similar to sucrose. However, miraculin is 400,000 times sweeter than sucrose in molar terms[12]. This compound is thermolabile which is inactivated above 100° C and below a pH of 3. The mechanism of action of miraculin has perplexed researchers for many decades. When the miracle berry is consumed before acidic foods like lemon, it can disguise the sour taste present in the foods and produce a sweet taste in the oral cavity which can linger up to 60 minutes from the time of consumption. Initially, researchers hypothesized that miraculin can cause a paralysis of tongue papilla, subsequently blocking sour taste receptors preventing the perception of sour taste and enhancing the sweet taste perception. Taste reception at low pH causes the induction of a sweet taste rather than an intrinsic suppression of sour perception[13].

The sweet taste receptors are comprised of 2 types of proteins namely the Type 1 membrane 2 (T1R2) coded by gene TAS1R2 and Type 1 membrane 3 (T1R3) coded by gene TAS1R3. Both of these sweet receptors are grouped under the G protein that helps to couple the taste receptor family. T1R2 responds to small molecules of sweet nature and T1R3 responds to larger molecules. The human sweet taste receptors have three categories: The Trans-Membrane Domain (TMD), the N-terminal segment Venus Flytrap Domain (VFD) followed by the Cysteine-rich Domain (CRD). The trans-membrane domain is responsible for signal transduction across cell membranes. Cysteine-rich domains are responsible for the structural integrity of receptors and the VFD domain is involved in ligand binding. Glucose and sucrose bind to the VFD domain of TAS1R2 and TAS1R3 subunits. Other sweeteners like aspartame bind to the VFD of the TAS1R2 subunit only[14]. The human sweet taste receptors and their classification is summarised in Figure 1.

Researchers have proposed a specific mechanism of action in the taste-altering property of miraculin which starts with the coating of the oral mucosa with miraculin. Then the carbohydrate portion of the miraculin molecule associates itself with the VFD domain of TAS1R1. This causes pH-dependent receptor activation. Partial activation of the sweet taste receptors occurs through extracellular acidification between extracellular protonated TAS1R2 and miraculin compound. The polypeptide chain of the miraculin compound contains histidine residues present in exposed regions which causes conformational change of the homodimers in miraculin.

Weak acidification initiates complete activation of the intracellular areas. The intracellular cascade begins with the TASR activation followed by the dissociation of Gβγ subunit from the Gα subunit (α-gustducin) of the heterotrimeric G protein followed by activation of phospholipase C- β2 (PLC-β2) which produces IP3. This IP3 interacts with its corresponding receptor (Type III IP3 receptor) which activates TRPMP5 and releases calcium ions from the endoplasmic reticulum. This is followed by the release of ATP by the opening of ATP channel Pannexin-1(PX1) that activates the gustatory afferent nerves. The taste fibres namely known as 'S-fibres' are responsible for conveying taste perception from T1R1 and T1R3 receptors which begin responding to sweet and acidic taste after taking miraculin. The mechanism of action of taste modification by miraculin is shown in Figure 2. When this neuronal signal carrying the sweet taste reaches the cortex of the brain, the sour taste entirely disappears. The sour modifying effects of the miracle berry are initiated under an acidic environment and last from 30 seconds to a maximum of 120 minutes after ingestion. This entire mechanism of action of miraculin is similar to the detection of other tastes like umami and bitterness[14,15].

Human beings have a strong preference towards foods that are predominantly sweet and salty. They naturally develop a strong aversion towards foods with a bitter and sour taste along with minor differences in individual preference based on psychophysiological factors. The bitter taste is associated with a high level of isothiocyanates derived from glucosinolates of certain vegetables. Isothiocyanates are rich in antioxidant, anti-inflammatory, anti-diabetic and chemotherapeutic properties. The phytochemicals in vegetables are loaded with dietary benefits and thus taking them can enhance the overall health status of patients. The bitter taste of vegetables can be masked with the use of miraculin. Similarly, certain fruits exhibit a sour taste due to the presence of organic acids. These organic acids have potent anti-inflammatory, and anti-obesity effects and help prevent osteoporosis[16]. Thus, miraculin can be used as an important component to sweeten food and mask the bitter and sour taste in vegetables and fruits. This can enhance the dietary intake of patients providing balanced nutrition.

In a study performed in 13 subjects, miraculin increases the sweet taste in a low-calorie dessert administered to the participants thus promoting energy compensation[17]. Another study was conducted in seven participants to record the cerebral cortex using Magneto-encephalography. The researchers stated that after taking miracle berries, the sour taste of citric acid was greatly decreased and sweet perception reached the primary taste region, a major part of the cerebral cortex[18]. A literature review by Divyapathogama *et al.* in 2024 explored that a total of 16 studies conducted with miracle berries and concluded that a total of five studies were effective in masking sour taste using sour acids, 4 studies successfully used miracle berries in juice or beverages and 6 studies incorporated it in foods. The taste-modifying properties were tested using citric acid as a sour acid (4 studies), lemon juice or as a lemonade as a sour beverage (4 studies) and lemon or lime in food items (6 studies). The literature review concluded that a total of 15 studies showed that miracle fruit increased sweetness and improved the food preferences among the participants. Earlier authors believed that the perceived sweetness intensity varies with the type of acid which is a major factor that determines the taste modifying property. Igarashi *et al.*, in 2013 observed that citric acid-based foods and solutions reacted effectively to miraculin's taste-modifying character when compared to acetic acid-containing solutions[19].

Miracle fruit has been explored as a sugar substitute in different food products like lemon-based popsicles, lemonade and beverages. It worked well in masking the sour flavours of the original food products. However, pilot studies have stated that since miraculin is a glycoprotein, it is deactivated in a thermal environment making it unsuitable for cooking. So, the best way to utilize miraculin is to use it as a flavouring agent to coat the oral cavity or tongue without incorporating it in routine cooking. Capitanio *et al.* in 2011 observed that miraculin could decrease bitterness in a binary combination of citric acid and caffeine. However, there are less than three studies which have evaluated miraculin's effect on bitter taste and further studies are needed to demonstrate its effects on different tastes[20,21]. Choi and Garza in 2021 demonstrated that miraculin increased the overall liking of yoghurt, cheese, and apple. It decreased the liking of lemonade and cucumber-based pickles in healthy adults. In diabetic and pre-diabetic adults too, miracle fruit had improved the liking for yoghurt, goat cheese, apple, lemonade,

and cucumber pickle. It also improved food intake among patients undergoing chemotherapy and enabled diabetic patients to reduce sugar and calorie intake[22,23]. Some discrepancies have been documented in different studies where certain participants showed an increase in liking for certain foods like lemonade after taking miraculin and some studies showed a decrease in liking for lemonade. Factors that can affect these taste alterations of miraculin are the dosage of miraculin, the type of food, gender and intrapersonal variations and differences in taste perception among the participants.

While miraculin is well established as taste-modifying glycoprotein, acting locally on the oral mucosa, its Pharmacokinetic (PK) and ADME (Absorption, Distribution, Metabolism, and Excretion) profile remains poorly characterized. Miraculin being a glycoprotein, its primary mechanism of action is through oral mucosal binding to the sweet taste receptor (T1R2/T1R3) at acidic pH. Current evidence suggests that miraculin acts locally on the tongue rather than exerting systemic effects. However, its stability in saliva, susceptibility to enzymatic degradation, and duration of receptor occupancy are incompletely understood. No robust data exist on systemic absorption, plasma bioavailability, or metabolic clearance in humans or animals. To advance clinical development, targeted PK/ADME studies are warranted, including *in vitro* assays on salivary protease stability, mucosal binding kinetics, and *in vivo* absorption and bio distribution studies. Such data are essential to clarify whether miraculin should be classified solely as a local nutraceutical or taste-modifying agent or if it has potential systemic pharmacologic roles.

6. Properties of Miracle Berry

6.1 Anti Diabetic Activity

Diabetes mellitus is a metabolic disorder where there is elevated blood glucose levels caused by abnormalities in carbohydrate, protein, and lipid metabolism due to insufficient insulin secretion or impaired insulin function. According to WHO, a total of approximately 529 million people will be diabetic in 2021, and the number will increase to more than double by 2050. Notably, about 40% of prescription medicines are derived from plant sources, and several plants exhibit pharmacological properties, including *S. dulcificum*. Previous studies have demonstrated the efficacy of Methanolic extract of *S. dulcificum* leaves (MSD) and Flavonoid-rich extract of *S. dulcificum* leaves (FSD) in normal and diabetic rats. The animals treated with MSD and FSD had lower serum glucose levels than the untreated diabetic controls. MSD and FSD also reduced glycated Haemoglobin (HbA1c) levels, interleukin-6 and tumour necrosis factor-alpha in fructose and streptozotocin-induced diabetic rats[24]. Furthermore, hepatic hexokinase activity was enhanced, and both extracts demonstrated inhibitory potential for glucose mediators. Studies using alloxan-induced diabetic male albino rats revealed reduced blood glucose levels following treatment with extracts of *S. dulcificum*. Oral administration of 50% *S. dulcificum* extracts resulted in a reduction in glucose levels (27.6 mg/dL and 34.0 mg/dL) respectively, while administration of 100% extracts led to reductions of 24 mg/dL and 28 mg/dL, respectively. Metformin was used as a positive control in this study, confirming the efficacy of both fruit and leaf extracts in lowering blood glucose levels[25]. Additionally, a recent study examined the anti-diabetic properties of ethanolic extracts of *S. dulcificum*. The study identified high phenolic content, particularly in the fruit flesh. Both the flesh and seed extracts effectively enhanced glucose uptake, as demonstrated by the 2-NBDG uptake test. These findings reveal the potential of *S. dulcificum* in diabetes treatment and its promising role in glucose metabolism regulation.

6.2 Anti Neoplastic Activity

The compounds like (þ)-syringaresinol and (þ)-epi-syringaresinol in *S. dulcificum* have antioxidant activity and also have inhibitory effects on cells causing skin cancer. In a study compounds like 4-acetonyl-3, 5-dimethoxy-p-quinol, p-hydroxybenzoic acid, cis-p-coumaric acid, trans-p-coumaric acid, and N-cis--feruloyl-tyramine inhibited tyrosinase activity in mushrooms. Tyrosinase inhibitor are utilized medically to treat hyper-pigmentation and is also incorporated in other cosmetics[26]. Another study conducted evaluated the effects of aqueous leaf extracts of *S. dulcificum* on mutations and oxidative damage induced by 2-Amino Anthracene (2-AA) and 4-Nitroquinoline-N-oxide (4-NQO). The results demonstrated a concentration-dependent inhibition of the mutagenicity of 2-AA (an indirect mutagen) and 4-NQO (a direct mutagen) in

Salmonella typhimurium strains TA98 and TA100. This antimutagenic activity was attributed to the phenolic constituents present in *S. dulcificum* leaves, which included syringic acid, trans-p-coumaric acid, veratric acid *etc*. The cytotoxic effects of *S. dulcificum* berry and stem extracts on colorectal cancer cell lines (HCT-116, HT-29), focusing on their impact on the expression of early apoptotic genes c-fos and c-jun. These genes encode Activator Protein-1 (AP-1), a class of transcription factors involved in key cellular processes such as proliferation, differentiation, and apoptosis. The study found that both berry and stem extracts significantly up-regulated the expression of c-fos and c-jun, leading to cytotoxic effects on colorectal cancer cells[27].

6.3 Anti Inflammatory Activity

Inflammation is a pathophysiological process characterized by swelling, impaired function, redness, pain and fever. Flavonoids, often referred to as nature's therapeutic agents, exhibit various pharmacological properties, including anti-inflammatory effects. These compounds have long been utilized in traditional medicine and the cosmetic industry as crude plant extracts. Numerous studies have demonstrated the anti-inflammatory properties of various flavonoid molecules in animal models, with some flavonoids found to regulate chronic inflammation and modulate immune cell extravasation into tissues. Several bioactive compounds in *Synsepalum dulcificum* including flavonoids, polyphenols, anthraquinones, cardiac glycosides, and tannins in leaf extracts, with similar compounds also detected in root extracts [28]. The anti-inflammatory mechanisms of flavonoids involve multiple molecular pathways, such as activating phase II detoxifying enzymes, and protein kinase C etc., Flavonoids also inhibit pro-inflammatory enzymes, including lipoxygenase, inducible nitric oxide synthase (iNOS), and cyclooxygenase-2 (COX-2), while suppressing the NF-κB signalling pathway. Inhibiting components of this pathway is a potential strategy for treating inflammatory disorders and cancer.

Cystic fibrosis is a genetic disorder caused by defective transmembrane conductance regulator channels, which leads to severe lung inflammation and excessive IL-8 production in lung tissues. Studies indicate that cardiac glycosides effectively reduce the hypersecretion of IL-8, mediated by NF-κB, in cystic fibrosis lung epithelial cells. Beyond their vascular functions, endothelial cells also regulate inflammation by controlling immune cell migration into tissues, a process that can be mitigated by cardiac glycosides[28].

6.4 Anti Convulsant Activity

The anticonvulsant property of *S. dulcificum* extract was assessed in mice which were subjected to pentylenetetrazole (PTZ), strychnine and maximal electroshock-induced seizures. PTZ is a noncompetitive GABA receptor antagonist that attaches itself to the receptor's picrotoxin site. Animals previously treated with miracle berry extract showed a significant resistance (33.33%) against PTZ and strychnine-induced convulsions, as well as a shorter recovery period following maximum electroshock-induced seizures. Because of its affinity for the GABA receptor's TX binding site, miraculous berry's inhibitory neurotransmission starts its anticonvulsant action[29].

6.5 Antioxidant Activity

Numerous antioxidants, including flavonoids, phenols, terpenoids, and amides, have been identified via research. In vitro tests of the miracle berry methanol extracts' antioxidant qualities revealed a strong antioxidant profile that can fend against oxidative damage. Antioxidant estimate techniques used included FRAP tests, DPPH (1, 1-diphenyl-2-picrylhydrazyl), ABTS, and others. According to a few research, glutathione S-transferase enzymes increased while hepatic malondialdehyde levels decreased. According to a 2016 study by Akinmoladun et al., the methanolic extract of miracle berry decreased the levels of hepatic malondialdehyde and serum total bilirubin. All the treated groups were given a subacute administration of the miracle berry extract (50-200 mg/kg). The results showed that the extract at doses lesser than 100 mg/kg can boost antioxidant defence and also provide hepatoprotective properties[30].

6.6 Hypolipidemic Activity

Hypolipidemic activity of miracle berry was evident in 2% ethanolic extract of the seeds, leaves and dry pulp. It has the property to decrease total cholesterol levels in the plasma due to active triterpenoids in the extracts. Huang et al 2020 evaluated the cholesterol-lowering

of miracle berries in hamster models which were fed with a 2% extract of miracle berry. Triterpenoids isolated from the seed extract namely Lupeol acetate and β-amyrin acetate decreased total cholesterol in hamsters[31].

6.7 Antimicrobial Activity

Synsepalum dulcificum has shown potent antimicrobial activity when evaluated by previous researchers. The MIC (minimum inhibitory concentration) values of two extracts of *S. dulcificum* fruits against gram-positive and gram-negative bacteria. Authors have documented that the petroleum ether extract of *S. dulcificum* had better microbial inhibitory action than the ethanol extract. The zone inhibition results also showed that there was potent antimicrobial activity against *Bacillus cereus, Staphylococcus albus, Staphylococcus aureus, Micrococcus luteus* and *Escherichia coli*[32].

6.8 Anti-hyperuricemic Activity

Increased blood uric acid levels of more than 6 mg/dl in women and more than 7 mg/dl in men are referred to as hyperuricemia. The production of uric acid is mediated by the enzyme xanthine oxidase. By blocking xanthine oxidase activity, miracle berries have strong anti-uraemic effects. "Allantoin" is the product of the catabolism of uric acid produced by xanthine oxidase. Mammals' synthesis of uric acid is directly inhibited by xanthine oxidase inhibition. The butanol extract of miracle berry fruit was used to lower the serum uric acid levels of mice that were given potassium salt to create hyperuricaemia. In RAW macrophages treated with monosodium urate (MSU), the butanol extract of miraculin also demonstrated xanthine oxidase activity. This property of miracle berry can be used to treat systemic diseases like gout [33].

6.9 Anti Alopecia Activity

Synsepalum dulcificum seed oil has been explored for its anti-alopecia activity, especially in healthy women with varying degrees of hair loss. Studies have shown that miracle berries are safe and effective in strengthening and repairing hair damage. The parameters like hair length and hair mass index were evaluated among the subjects. The study results stated that there was significant hair growth with an increase in hair mass and hair index within a period of 4 to 8 months of seed oil usage. Miracle berry seed oil has emerged as the natural choice for the treatment of women having a history of alopecia [34].The various recent human clinical studies and randomized controlled trials evaluating *Synsepalum dulcificum* in taste disorders, metabolic conditions, and cancer-related nutrition are summarised in Table 3.

7. Distinction of Bioactivities by Source

While *Synsepalum dulcificum* has been widely studied for its diverse pharmacological and nutritional benefits, it is essential to distinguish between activities attributed to different plant components.

7.1 Miraculin (Glycoprotein)

Functions as a taste-modifying agent by binding to the human sweet taste receptor (hT1R2-hT1R3). Its primary application is in improving palatability of sour or metallic-tasting foods, with potential utility in managing chemotherapy-related taste disorders and in low-calorie dietary interventions. To date, no direct antioxidant, anti-inflammatory, or metabolic effects have been experimentally demonstrated for purified miraculin [35].

7.2 Crude Extracts (Pulp, Seed, Leaf, Root; Aqueous/Ethanolic/Methanolic)

Rich in phenolics, flavonoids, alkaloids, and terpenoids. These extracts have shown **antioxidant** (free radical scavenging**),** anti-inflammatory (reduction of pro-inflammatory cytokines), **anti-diabetic** (improving insulin sensitivity, lowering blood glucose), hepatoprotective, and antimicrobial effects in preclinical models.

7.3 Isolated Phytochemicals

Flavonoids and phenolic acids (e.g., catechin, epicatechin, quercetin derivatives) contribute significantly to antioxidant and anti-inflammatory activities. Alkaloids and terpenoids from the seeds and leaves have been implicated in antimicrobial and metabolic effects[36]. Table 4 maps each reported biological activity of *Synsepalum dulcificum* to its source whether attributable to miraculin, crude extracts, or specific isolated phytochemicals highlighting

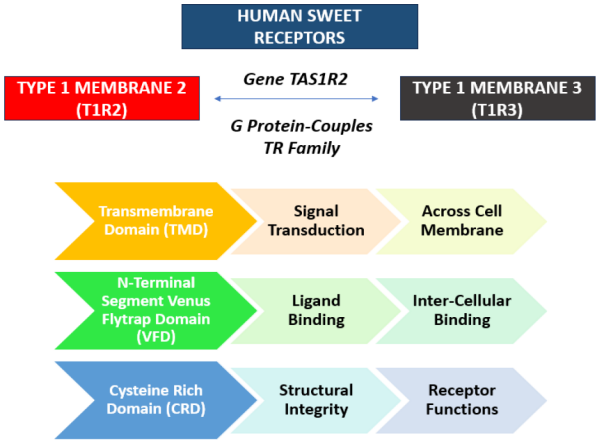


Figure 1. The different human sweet taste receptors, their classifications and their functions in taste perception.

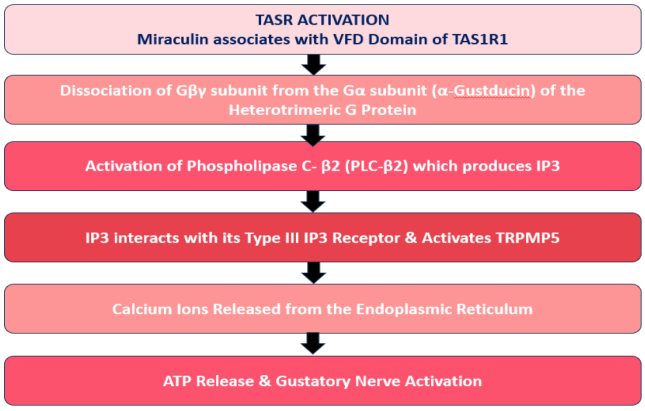


Figure 2. The mechanism of action of miraculin and the chemical receptors involved in modifying the taste perception activity.

Table 1. Major phytochemical constituents of miracle berry

S. No.	Part of the Plant	Phytochemicals Identified
1	Stem	Dihydro-feruloyl-5-methoxytyramine Syringaresinol Vanillic acid N-Feruloyl tyramine Epi-syringaresinol
2	Leaves	Cyanidin-3-monoglucoside Delphinidin-3-monoarabinoside Cyanidin-3-monoarabinoside Delphinidin-3-monogalactoside β-Sitosterol Stigmasterol Lupeol Lupenone α-Tocopheryl Quinone Quercetin Kaempferol Catechin Polyphenols
3	Roots	p-hydroxybenzoic acid Vanillic acid Syringic acid
4	Fruit	**Vitamins** A, C, D, E, and K Essential amino acids: lysine, leucine, isoleucine, phenylalanine, threonine, histidine, valine, tryptophan Nonessential amino acids: glycine, proline, tyrosine, glutamic acid *etc.*
5	Seed Extract	**Pentacyclic Triterpenes** Lupenyl acetate β-amyrin acetate

Table 2. Different parts of *S. Dulcificum*

Leaves	
Stem	
Flowers	
Fruit	
Seed	

Table 3. Recent human clinical studies and randomized controlled trials evaluating *S. dulcificum* (miracle fruit) in taste disorders, metabolic conditions, and cancer-related nutrition

Study	Design	Population	N	Intervention	Outcomes	Key Findings
Wilken and Satiroff[37]	Pilot, crossover placebo-controlled.	Cancer patients undergoing chemotherapy with taste alterations.	8	Miracle fruit supplement *vs* placebo (2-week periods)	Self-reported taste change; food intake diary.	All participants reported taste improvements with the Miracle fruit; improved palatability of foods.
Choi and Park[38]	Randomized crossover trial, placebo-controlled.	Adults with diabetes or prediabetes.	50	Miracle fruit tablet *vs* placebo taken ~10 min before sour-tasting foods.	Liking (hedonic scale), calorie intake, acceptability.	MF increased liking of sour foods; acceptable in taste, potential for use in weight-loss or dietary management.
Lopez-Gil[39] CLINMIR pilot study (efficacy and safety)	Triple-blind, randomized, placebo-controlled RCT.	Malnourished cancer patients under active antineoplastic therapy.	31	Daily DMB (standard dose 150 mg or high dose 300 mg) *vs* placebo for 3 months.	Electrochemical taste perception, nutritional status, quality of life, energy intake, body composition.	Standard dose DMB improved taste acuity, energy intake, fat-free mass, QoL; no safety concerns.
Soares *et al.*[40] "Treatment of taste alterations in chemotherapy patients using the 'miracle fruit': Preliminary analysis".	Crossover pilot RCT	Chemotherapy patients with self-reported dysgeusia.	23	Miracle Fruit (fresh fruit) *vs* supportive measures alone (crossover after 2 weeks).	Taste change (Wickham questionnaire), weight, QoL.	~30-35% of patients reported taste improvement; no significant weight change; safe with only mild discomfort.
Parker and Velargo[41] "*S. dulcificum* and varied taste occurring post-radiation trial"	Double-blind randomized trial.	Head or neck cancer patients with post-radiation gustatory dysfunction.	16	Miracle fruit *vs* placebo for 1 month.	Taste batteries, questionnaires, weight change.	Over half reported sweet taste was most affected; subjectively MF improved taste; measured taste or sour misidentification; modest weight changes.

Table 4. Mapping of reported bioactivities of *S. dulcificum* to their specific source (miraculin, crude extract, isolated phytochemical)

Reported Activity	Miraculin	Crude Extract	Specific Phytochemicals
Taste modification	(Glycoprotein binding to sweet receptor)	-	-
Antioxidant	-	(Pulp, seed, leaf extracts)	Flavonoids, phenolics (catechin, quercetin)
Anti inflammatory	-	(Leaf/seed extracts *in vitro* and *in vivo*)	Phenolics, terpenoids
Anti diabetic	-	(Pulp/leaf extracts, animal models)	Flavonoids, alkaloids
Hepatoprotective	-	(Extract studies in rodents)	Phenolic acids
Anti microbial	-	(Leaf, seed extracts)	Alkaloids, terpenoids
Anti cancer (supportive nutrition *vs* cytotoxicity	(Taste improvement aiding nutrition in cancer patients)	(Seed/pulp extracts show cytotoxicity *in vitro*)	Flavonoids, saponins
Nutritional supplementation	(Improves taste perception, calorie intake)	(Nutrient-rich pulp/seed)	Vitamins, amino acids

that pharmacological effects are primarily extract or phytochemical driven, whereas miraculin's role is confined to taste modification.

Although *Synsepalum dulcificum* demonstrates promising pharmacological and nutritional potential, systematic safety evaluations remain limited. Current evidence is largely preclinical and does not meet Good Laboratory Practice (GLP) standards. Well-designed GLP-compliant toxicity studies are required to establish acute, sub-chronic, and chronic safety profiles of both crude extracts and isolated compounds. In addition, since miraculin and polyphenol-rich extracts may alter taste perception and metabolic pathways, drug–nutrient and drug–drug interaction screens are essential to rule out potential contraindications, particularly in patients receiving polypharmacy (e.g., oncology or metabolic disorders). These studies are critical for supporting regulatory approval and for translating *S. dulcificum* into safe nutraceutical or therapeutic applications.

8. Conclusion and Future Prospective

Synsepalum dulcificum is a plant with remarkable biological, phytochemical, and pharmacological properties. This review has highlighted its diverse bioactive constituents, including flavonoids, alkaloids, terpenoids, and the unique glycoprotein miraculin, which plays a significant role in taste modification. The plant exhibits a wide range of pharmacological activities, including antioxidant, anti-diabetic, anti-inflammatory, antimicrobial, and hepatoprotective effects, demonstrating its potential as a valuable therapeutic agent which is completely natural. Despite its promising applications, extensive pharmacological research and clinical trials are required to fully understand its mechanisms of action, dosage, and long-term safety. Given the increasing global interest in plant-based medicine and nutraceuticals, *S. dulcificum* presents a significant opportunity for further development in the pharmaceutical and food industries. Future studies should focus on isolating and characterizing its active compounds, evaluating their bioavailability, and determining the potential for various other therapeutic applications. Further clinical studies are required to validate the efficacy, safety, and underlying mechanisms of miraculin while emphasizing the importance of advanced research to fully uncover its pharmacological applications in modern medicine. By bridging the gap between traditional knowledge and modern scientific research, *S. dulcificum* could contribute to the development of novel, plant-derived treatments for various health conditions, reinforcing its role as a valuable medicinal plant.

9. Author Contribution

Anuradha Ganesan (AG) conceptualized the review, designed the framework, and supervised the overall work. Jeevitha Gauthaman(JG) performed the literature search, data extraction, and drafted the initial manuscript. Krishnan Hari (KH)contributed to data interpretation, critical revision of the manuscript, and provided intellectual input. All authors reviewed, edited, and approved the final version of the manuscript.

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