MS EDITIONS

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BOLETIN LATINOAMERICANO Y DEL CARIBE DE PLANTAS MEDICINALES Y AROMÁTICAS
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Revisión / Review

A comprehensive review on chemical and pharmacological potential of *Synsepalum dulcificum* (Schumach. & Thonn.) Daniell

[Revisión comprensiva del potencial químico y farmacológico de *Synsepalum dulcificum* (Schumach. & Thonn) Daniell]

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Section Review

Received: 7 September 2023
Accepted: 12 October 2023
Accepted corrected: 22 March 2024
Published: 30 September 2024

Citation:
Afzal S, Manap ASA, Zelynn C
A comprehensive review on chemical and pharmacological potential of Synsepalum dulcificum (Schumach. & Thonn.) Daniell
Bol Latinoam Caribe Plant Med Aromat
23 (5): 706 - 731 (2024)
https://doi.org/10.37360/blacpma.24.23.5.44

Abstract: The fruit of plant *Synsepalum dulcificum* (Schumach. & Thonn.) Daniell, is found native to tropical regions of West Africa, and vernacularly recognized as the “Miracle Fruit” by Africans. The property of the plant has traditionally been employed in many food industries, besides its ethnopharmacological significance. The phytochemical analysis from literature reveals that various parts of plant contains many bioactive components including alkaloids, lignans, phenolic acids, glycoproteins and flavonoids. Recent studies exhibit its pharmacological potential such as antidiabetic, antihyperlipidemic, anti-cancer, antimicrobial, antioxidant, anti-hyperuricemia and anti-convulsant properties. Therefore, this review aims to systematically summarizes scientific evidences with the therapeutic, ethnopharmacological and traditional claims found in literature. However, the data acquired is still very imperfect, thus future research is hopeful to discover the precise mechanism of action of its bioactive components to explore chemical constituents, and their nutraceutical and clinical uses of this multipurpose plant to employ its valuable effects on human beings.

Keywords: *Synsepalum dulcificum*; Traditional uses; Phytochemistry; Pharmacology

Resumen: El fruto de la planta *Synsepalum dulcificum* (Schumach. & Thonn.) Daniell, se encuentra de forma nativa en las regiones tropicales del África Occidental, y es reconocida vernáculamente como la "Fruta Milagrosa" por los africanos. La propiedad de la planta ha sido empleada tradicionalmente en muchas industrias alimentarias, además de su significancia etnofarmacológica. El análisis fitoquímico de la literatura revela que varias partes de la planta contienen muchos componentes bioactivos incluyendo alcaloides, lignanos, ácidos fenólicos, glicoproteínas y flavonoides. Estudios recientes exhiben su potencial farmacológico como propiedades antidiabéticas, antihiperlipidémicas, anticancerígenas, antimicrobianas, antioxidantes, anti-hiperuricémicas y anticonvulsivas. Por lo tanto, esta revisión tiene como objetivo resumir sistemáticamente las evidencias científicas con las afirmaciones terapéuticas, etnofarmacológicas y tradicionales encontradas en la literatura. Sin embargo, los datos adquiridos aún son muy imperfectos, por lo que se espera que futuras investigaciones descubran el mecanismo de acción preciso de sus componentes bioactivos para explorar los constituyentes químicos y sus usos nutracéuticos y clínicos de esta planta multiusos para emplear sus valiosos efectos en los seres humanos.

Palabras clave: *Synsepalum dulcificum*; Usos tradicionales; Fitoquímica; Farmacología

INTRODUCTION

Medicinal treatments through the exploitation of plant-based natural compounds are widely investigated and numerous plants as well as herbs have been proclaimed already for their employments as various traditional remedies. Medicinal food plants belonging to Sapotaceae family are widely used in diet from the ancient time and are also having importance in ethnomedicinal system for the treatments of several ailments.

Taxonomic classification

Synsepalum dulcificum (Schumach. & Thonn) Daniell is a member of the Kingdom: Plantae, Subkingdom: Viridiplantae, Infrakingdom: Streptophyta, Superdivision: Embryophyta, Division: Tracheophyta, Subdivision: Spermatophytina, Class: Magnoliopsida, Order: Ericales, Family: Sapotaceae, Genus: Synsepalum (A. DC.) Daniell, Species: Synsepalum dulcificumm (Ogunsola & Ilori, 2008; Inglett & Chen, 2011; Chen *et al*., 2012; Lim, 2013; Achigan-Dako *et al*., 2015; Njoku *et al*., 2015; Ricardo & Chacón, 2015; Jian *et al*., 2017; Tchokponhoué *et al*., 2017; Seong *et al*., 2018; Akinmoladun *et al*., 2020). The plant *Synsepalum dulcificum* (Schumach. & Thonn) Daniell name is the accepted name of a species in the genus *Synsepalum* (family Sapotaceae) according to "The Plant List", and this name has been checked and confirmed with the **http://www.theplantlist.org** database source. Since *Synsepalum dulcificum* (Schumach. & Thonn) Daniell was first discovered in the tropical region of West Africa, and there were a few names that were given to this plant by the natives. It was also called as Agbayun as well as Uni by the native Africans. Apart from that, *Synsepalum dulcificum* (Schumach. & Thonn) Daniell was also referred to as miracle berry, miraculous berry, *Bakeriella dulcifica*, *Bumelia dulcifica*, *Richadella dulcifica*, *Sideroxylon dulcificum*, and miraculin among other common names. This plant was later on also found as exotic species in other regions of Africa as well as in other countries, where this plant was given many different names, such as, Asowa (Twi, Ghana), Ele (Ewe, Ghana), Fruit Miraculaix (French), Wunderbeere (German) and Taami/Asaa/Ledidi (West Africa) (Inglett & Chen, 2011; Lim, 2013; Jeremiah *et al*., 2015a; Akinmoladun *et al*., 2020).

Geographical distribution and morphological properties

Initially, this plant was found native to the tropical region of west and west central of Africa. This plant was cultivated from Ghana to Nigeria, experimental plantations in tropical America, as well as many Southeast Asian countries, Australia and United States of America (USA). As a matter of fact, in the latest research by Xingwei et al, it was observed that *Synsepalum dulcificum* (Schumach. & Thonn) Daniell had been largely cultivated in the regions of Taiwan as well as Japan in order to be used in the food industries due to its potential for taste modification (Wilken & Satiroff, 2012).

The shrub has dense foliage and many branches and grow to 6-15 feet tall. From December to June, it will yield ripe red berries which are ellipsoidal about 0.75 inch in length. It features a huge seed encased in a thin sheet of berry flesh with a slight cherry flavour (Inglett & May, 1968). The simple oval leaves which have smooth margins and a waxy underside grow in spiderlike clusters at the ends of tiny branches. The plant also bears red drupe fruits which are around 2-3 cm (0.8-1.2 inches) in length and are grown from the small white flowers. In acidic soil, plants begin to bear fruit after three or four years (Chen *et al*., 2009).

Traditionally, the fruit, leaves as well as the stems of this plant were used in many daily activities as well as in folk medicines, especially employed in Africa. One of the traditional applications of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell fruit as mentioned earlier was for taste modification. In Benin, West Africa, this property was used in order to help the natives to consume tart as well as sour fruits. Whereas in Ghana, Africa, this miracle berry was incorporated into their daily dishes as well as in beverage preparations (Inglett & May, 1968). A good example of food that was sweetened by miracle berry in Africa were maize bread, palm wine as well as local beer. Usually, the fruit was chewed right before consuming any sour food and the food tasted sweet. This sweet perception of sour food was reported to last from 30 minutes up to 1 hour after chewing the miracle fruit (Inglett & Chen, 2011).

Apart from taste modification, *Synsepalum dulcificum* (Schumach. & Thonn) Daniell also have many applications in folk medicine. In Benin, West Africa, the leaves of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell were used widely to treat diabetes, hyperthermia, malaria and enuresis. In addition, the seed was used to treat obesity as well as stomachache and anemia. The root on the other hand was used to treat cough especially that associated with tuberculosis. The bark was found useful in treatment of disease related to the prostate. Traditionally, the branches and the twigs of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell were also important. The branches were used as hoe and rakes by the farmers, while the twigs were used as toothbrushes (Inglett & Chen, 2011).

Phytochemical profile

Synsepalum dulcificum (Schumach. & Thonn) Daniell which is also known as Miracle Fruit/Miracle Berry, is plant that is famous worldwide due to its property of taste modification. Due to this reason, this plant has been said to be a miracle plant or miracle berry. Usually, this property of taste modification is due to the presence of miraculin, which is a type of glycoprotein that can be extracted from the fruit part (particularly from the pulp) of this plant. The glycoprotein miraculin is able to cause the perception of taste to be altered, where sour food will taste sweet due to miraculin's action on tastebuds. Miraculin bind to the taste buds to activate the sweet receptors hence cause the sweet taste. This reaction favors at low pH and this effect can last up to 60 minutes until it fades and eliminates by saliva. In addition, miraculin is also useful in controlling obesity when administered orally and improve insulin sensitivity. Miraculin also use in food and beverage in some area to make the food more palatable, it increases the sweetness without increasing the energy compensation or super intake which suitable for diabetic people (Ogunsola & Ilori, 2008; Chen *et al*., 2010a; Chen *et al*., 2012; Achigan-Dako *et al*., 2015; Jeremiah *et al*., 2015a; Njoku *et al*., 2015; Jian *et al*., 2017; Tchokponhoué *et al*., 2017; Seong *et al*., 2018; Akinmoladun *et al*., 2020).

There is a wide array of vitamins and minerals that are contained in *Synsepalum dulcificum* (Schumach. & Thonn) Daniell, particularly in the seed of the miracle berry (Lim, 2013). *S. dulficum* contains vitamin A, C, E, folic acid, and some essential and non-essential amino acids which give its additional benefits. The phenolic compound and flavonoids give multiple biological effect. The flavonoids and saponins in this plant are also a type of dietary fiber that found in the plant which can improve glycaemia, lower good pressure and drum cholesterol level of individuals. The attention of the plant increases as it has demand in food and pharmaceutical industry.

Synsepalum dulcificum (Schumach. & Thonn) Daniell also contains anthocyanin which is found in abundance in the fruit pulp as well as the peel of the miracle berry. These anthocyanins have properties of a good antioxidant and also it is rich in color pigments. These properties are modernly used in the food industries, where the color pigment of anthocyanin are used as coloring agent in food. The color changing ability of anthocyanins present in *Synsepalum dulcificum* (Schumach. & Thonn) Daniell fruit is comparable to the synthetic FD & C Red No. 2 coloring agent used in food industries. Since anthocyanin also have antioxidant properties, it is used widely in the making of carbonated drinks where they enhance the stability of the drinks by reducing the potential of oxidation (Wilken & Satiroff, 2012).

The mineral content of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell was studied. The mineral concentration of the leaf extracts: calcium (0.001 ± 0.00) mg/100 g, chromium (0.0006 ± 0.00) mg/100 g, iron (0.0029 ± 0.01) mg/100 g, zinc (0.0095 ± 0.00) mg/100 g and copper (0.00082 ± 0.01) mg/100 g while the root extracts: calcium (0.00134 ± 0.01) mg/100 g, chromium (0.00073 ± 0.01) mg/100 g, zinc (0.0097 ± 0.01) mg/100 g, iron (0.00025 ± 0.01) mg/100 g and copper (0.007 ± 0.01) mg/100 g (Osabor *et al*., 2016).

Many mineral elements were identified (in mg/100 g) in the seed including, 569.500 ± 2.820 potassium, 72.170 ± 5.340 calcium, 25.000 ± 0.000 sodium, 17.630 ± 0.390 magnesium, 3.050 ± 0.490 iron, 2.710 ± 0.009 zinc, 2.420 ± 0.008 copper, 2.380 ± 0.004 manganese, 0.240 ± 0.028 nickel and 0.013 ± 0.002 cadmium (Jeremiah *et al*., 2015a). The amino acid profile and vitamin contents of the pulp of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell berry were identified. The amino acids identified (in g/100 g protein) in berry were lysine (1.60), leucine (2.35), isoleucine (0.82), tyrosine (0.92), phenylalanine (1.25), threonine (0.52), valine (0.52), methionine (0.31), proline (0.59), glycine (0.38), alanine (1.01), cysteine (0.45), serine (0.77), glutamic acid (3.43), arginine (1.94), histidine (0.62) and aspartic acid (1.76). The study revealed that the vitamin A, C and E content were 2.54 ± 0.27 mg/100 g, 1.33 ± 0.24 mg/100g and vitamin E 0.78 ± 0.05 mg/100 g respectively (Njoku *et al*., 2015).

The physicochemical parameters of seed extracts: 38.08% moisture content, 19.47% crude protein, 11.94% crude fat, 29.08% total carbohydrate, 0.66% crude fibre and 1.43% ash (Jeremiah *et al*., 2015b). The leaf and fruit extracts of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell contained carbohydrate 40.38 and 17.44%, crude fibre 17.58 and 3.63%, crude protein 8.42 and 10.46%, crude fat 1.97 and 2.32%, ash content 2.87 and 3.95% and moisture content 28.78 and 62.40% respectively) (Awotedu & Ogunbamowo, 2019a; Awotedu & Ogunbamowo, 2019b). The proximate analysis of the leaves extracts of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell showed protein 6.62 ± 0.02%, crude lipid 12 ± 2.00%, crude fibre 17.5 ± 0.50%, moisture 40.30 ± 1.53%, ash 6.70 ± 2.00% and carbohydrate 57.60 ± 0.01%, while the roots extracts showed protein 5.6 ± 0.07%, crude lipid 7.5 ± 1.4%, crude fibre 20.30 ± 1.53%, moisture 29.2 ± 1.06%, ash 8.00 ± 1.56% and carbohydrate (58.60 ± 0.01)% (Osabor *et al*., 2016). The studies found appears to be in agreement with a recent study on the proximate study of the fruit of *S. dulcificum* (Fadeyibi *et al*., 2021).

From the previous studies, the extraction from different parts of the *Synsepalum dulcificum* (Schumach. & Thonn) Daniell plant had isolated many useful bioactive compounds, such as alkaloids, lignans, phenolic acids, glycoproteins, oils substances, phytosterols, triterpenes, and colour pigment flavonoids. These phytochemicals had been employed in the food industries as well as in the field of pharmacology and cosmetology. In a recent study, seventeen compounds were isolated for the first time from *S. dulcificum*. Notably, compounds named 7S, 8R)-dihydrodehydrodiconiferyl alcohol, (7S, 8R)-dihydrodehydrodiconiferyl alcohol-9-β-D-glucopy-ranoside, quercetin and quercetin-3-O-glucoside exhibited significant antioxidant properties (Wang *et al*., 2020). The preliminary phytochemical analysis showed that *Synsepalum dulcificum* (Schumach. & Thonn) Daniell pulp contained saponin, flavonoids, tannin, alkaloids, glycosides, phenol, resins, terpenoids, steroids, and anthraquinones and cyanogenic glycosides (Ibrahim *et al*., 2020; Awotedu *et al*., 2021). The isolated compounds from *Synsepalum dulcificum (Schumach. & Thonn) Daniell* are presented in Table No. 1.

Pharmacological potential of Synsepalum dulcificum (Schumach. & Thonn) Daniell

Treatment of Dysgeusia

In simple words, dysgeusia is alteration of taste. This is not an uncommon side effect that is experienced by patients that are undergoing anticancer therapy. However, till date there is not a single agent that can be used in order to prevent or reduce the occurrence of dysgeusia. Usually, patients that are undergoing cancer treatment will complaint of some metallic taste in their mouth which makes their eating experience unpleasant. This sometimes causes the patients to refuse to eat as the food tastes spoilt, which indirectly will cause these patients to be prone to malnutrition, weight loss and reduced quality of life. The fruit of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell have been studied by a few researchers and pilot tests had been conducted in patients that had dysgeusia. Most of the studies (as discussed below) hypothesize that since miracle fruit has taste modification properties, it shall to some extent help with reduction of dysgeusia in the patients receiving cancer chemotherapy.

The effect of fruit of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell on dysgeusia was pilot studied by Soares *et al*. (2010), where 23 patients whose performance score was 2 or below, and were also on oral chemotherapeutic agents and complained of experiencing dysgeusia were used as their sample size (Soares *et al*., 2010). The aim of the study was to investigate whether, miracle berry can help in taste improvement and weight stabilization in the patients experiencing dysgeusia. The patients were divided into Group A (received miracle berry and supportive therapy for first 2 weeks, and then only supportive therapy for the next 2 weeks), and Group B (received supportive therapy only for the first 2 weeks, and then miracle berry and supportive therapy for the next 2 weeks). From the sample of 23 patients, only 56% of the patients completed the study. 52% of the patients reported that they had at least some stabilization in taste after taking the miracle berry and 30% of patients reported to have improvement in taste. However, there was no significant change in weight observed throughout this study.

Next, the effects of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell on post irradiation gustatory dysfunction (PIGD) was studies by Velardo & Samant (2012), where they stated that PIGD is one of the main reasons for occurrence of malnutrition in patients that undergo head or neck radiotherapy.

Radiotherapy in the head or neck region can cause disturbance in taste in the patients (Velardo & Samant, 2012). The aim of this study was to investigate whether *Synsepalum dulcificum* (Schumach. & Thonn) Daniell was of any significance in PIGD as well as weight stabilization of the patients. 16 patients who had complaints of dysgeusia were randomly selected and randomly assigned into the trial group (receive the miracle berry) and control group (received placebo) and their weight pre- and post-trial was measured. After a period of 1 month, the participants were asked to answer some questions in a questionnaire and the data was analyzed, where 54% of the patients in trial group reported of having improvement in their taste ability compared to the control group. However, from the aspect of weight, there was no statistically significant change in weight observed throughout this study between the treatment and control group.

Wilken & Satiroff (2012), conducted a pilot study on miracle fruit as a novel supportive intervention on eight cancer patients who reported taste changes while receiving chemotherapy. The goal of this pilot trial was to identify if consuming the Miracle Fruit supplement could help with chemotherapy-related taste changes, therefore enhancing food taste and ultimately leading to better nutrition. Four of the subjects received a two-week supply of the supplement, while the remaining four received a placebo. The supplement group received a two-week supply of the placebo after two weeks, whereas the placebo group received a two-week supply of the supplement. The supplement caused significant taste modifications in all of the trial participants (Wilken & Satiroff, 2012).

Antimicrobial potential

Wasoh *et al*. (2018), mentioned that Synsepalum dulcificum (Schumach. & Thonn) Daniell exhibited antibacterial activity. In this study young and mature Synsepalum dulcificum (Schumach. & Thonn) Daniell's leaves using methanol and ethanol as the solvents revealed that yield of methanolic extract of mature leaves (25.35%) was higher than young leaves (25.26%). Similarly, ethanolic extract of mature leaves (14.66%) yield was also the highest but it was lesser as compared to methanolic yield. The antibacterial activity was analysed against pathogenic bacteria called *Listeria monocytogenes*. *L. monocytogenes* resistant to many antibacterial medicines, thus finding a compound to against this bacterium is very though (Kümmerer, 2009; Abbasiliasi *et al*., 2014; Wasoh *et al*., 2018). However, in this study, the extract was found capable of exhibiting antibacterial effect towards *L. monocytogenes*. These findings indicate that methanolic extract of mature leaves (284.74 mm^2/mL) achieved higher antibacterial activity than mature leaves (271.47 mm^2/mL) with same extraction. For young leaves, methanolic extract showed antibacterial activity of 159.06 mm^2/mL while ethanolic extract showed antibacterial activity of 232.59 mm^2/mL. This showed for young leaves, ethanolic extract exhibited greater antibacterial activity than methanolic extract. In short, methanolic extract of mature leaves showed the highest yield and greatest antibacterial action (Wasoh *et al*., 2018). Besides, a study conducted by Lateef *et al.* (2016) used extract of leaves and seeds of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell for photosynthesis of silver nanoparticles (AgNPs). AgNPs is believed to have potential to kill bacteria by interacting with cell wall constituent's sulphur and phosphorus. This action induces killing by interrupting growth, reproduction and respiration of bacteria (Rai *et al*., 2009). The extracts were found enable to catalyse the development of AgNPs. Inhibition of growth of drug resistant bacterial strains like *Pseudomonas aeruginosa* and *Klebsiella granulomatis* reflected as inhibition zone between 11 to 24 mm with Minimum Inhibitory Concentration (MIC) of 60 μg/mL. Likewise, biosynthesized AgNPs using miracle plant's leaves and seeds extracts exhibited outstanding activity against fungal like *A. flavus* and *A. niger* with 100% of growth inhibition. For *A. fumigatus*, the suppression of growth produced by leaves was 75.60% and 73.17% for seeds. The antifungal action was conveyed by the attack of cell wall and demolition of spores thus leading to intracellular constituent outflow and eventually death (Lateef *et al*., 2016). Recent study evaluated the antimicrobial effects of the leaves of *S. dulcificum* (Ibrahim *et al*, 2020). The study showed that the activity of *S. mutans* and *S. sobrinus* have been inhibited by the water extract of *S. dulcificum* leaves. The leaves of *S. dulcificum* showed antibacterial activity which been used to studies against oral pathogen for the first time. Another study evaluated the antimicrobial effects of the fruit of S. dulcificum (Afzal et al., 2021). For this study, it showed that the ethanol extract of S. dulcificum has better inhibition zone than petroleum ether extract for *S. aureus*, *B.*

subtilis and *P. vulgaris*.

In addition, essential oil can be obtained from leaves of the miracle plant. It displayed antibacterial action against gram positive and also gram-negative bacteria. The essential oil obtained from miracle plant's leaves was able to constrain the experimental bacteria growth as reflected by zone of inhibitions. The experimental bacteria tested namely *Bacillus subtilis* 17.50 ± 0.8 mm, *Bacillus cereus* 6.02 ± 0.7 mm, *Staphylococcus albus* 5.14 ± 1.2 mm, *Staphylococcus aureus* 4.21 ± 1.0 mm, *Micrococcus tetragenus* 16.92 ± 0.7 mm, *Micrococcus luteus* 3.43 ± 0.6 mm and *Escherichia coli* 14.60 ± 1.0 mm (Lu *et al*., 2014).

Antidiabetic activity

Diabetes mellitus (DB) can be defined as a metabolic disorder that lead to high blood sugar level as a result of modification in carbohydrate, proteins and lipids metabolism caused by insufficient of insulin secretion or abnormal of insulin activity (Ahmad *et al*., 1991). According to WHO (2011), statistic shows that over 346 million of people who have been diagnosed with DB, majority fall in type 2 diabetes mellitus and type 1 diabetes mellitus only account for 10%. According to Global diabetes report from WHO (2015), almost 1.5 million deaths were due to diabetes mellitus in 2012. In actual fact, approximately 40% of prescription medicines are from flora origin. Some flora possesses pharmacological activity such as *Synsepalum dulcificum* (Schumach. & Thonn) Daniell. *Synsepalum dulcificum* (Schumach. & Thonn) Daniell or in the other name, miracle fruit, magic fruit, miraculous or flavor fruit is found to have antidiabetic effect (Obafemi *et al*., 2017a).

From the result obtain by the previous studies which use methanol extract of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell leaves (MSD) and flavonoid-rich extract of S. dulficicum leaves (FSD) on normal control and diabetic induced Wistar albino rats. The group using MSD and FSD showed positive result in lowering the serum glucose level compared to diabetic control group. Diabetic groups when administered with 30 mg/kg MSD have difference of 0.29 between the day 1 which was 78.43 mg/dL and day 21 which was 78.14 mg/dL. However, the result of day 21 of administration of 60mg/kg MSD in diabetic group increase 0.48 mg/dL from day 1 of 73.43 mg/dL. There was significant increase of 3.17 when diabetic group was administered with 30 mg/kg of FSD on the day 21 with 77.03 mg/dL. The result Diabetic rats when administered with 60 mg/kg FSD shown positive result as the significant decrease in blodd glucose levels between day 1 and day 21 was 79.00 and 72.89 mg/dL respectively (Obafemi *et al*., 2017a).

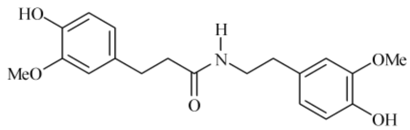
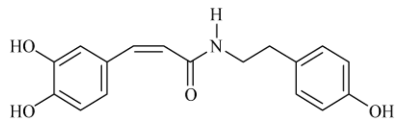
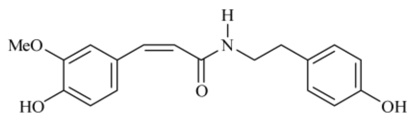
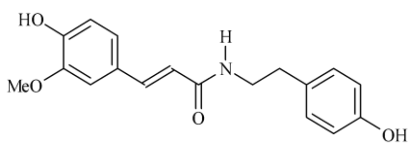
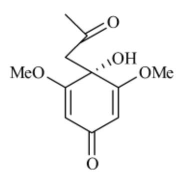
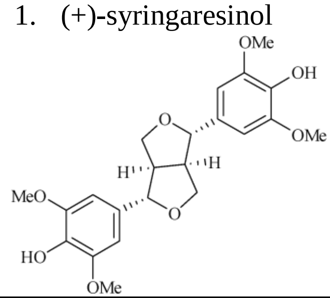
MSD and FSD had also reduced the HbA1c and serum level of interleukin-6 as well as TNF-α in fructose and streptozotocin induced diabetic rats. Moreover, hepatic hexokinase activity was raised and had proven that MSD and FSD extract possess the ability of α-amylase and α-glucosidase inhibition (Obafemi *et al*., 2019).

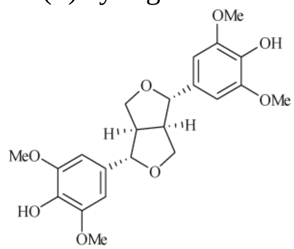
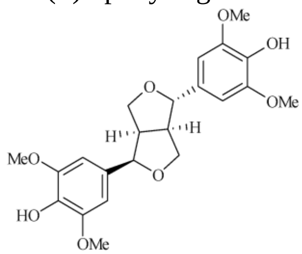
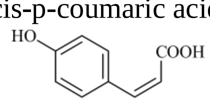
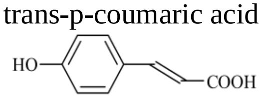
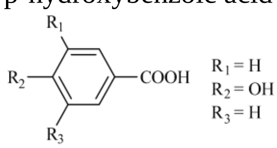
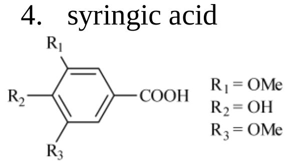
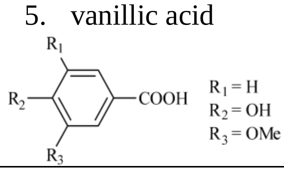
By using alloxan-induced diabetic male albino rats, after treatment with fruit and leaves extract of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell, there is a significant decrease in blood sugar level. Oral gavage administration of 50% of fruit and leaves extract of Synsepalum dulcificum (Schumach. & Thonn) Daniell were able to decrease the blood glucose level by 27.6 mg/dL and 34.0 mg/dL respectively whereas oral administration of 100% of fruit and leaves extract of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell managed to reduce the blood glucose level by 24 mg/dL and 28 mg/dL respectively. In this study, metformin was used as standard drug for positive control group. Hence both extracts from fruit and leaves of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell are found to exhibit blood sugar lowering effects in alloxan-induced male albino rats (Dioso *et al*., 2016). Another recent study evaluated the antidiabetic effects of seed and fruit flesh ethanolic extracts of *S. dulcificum* (Han *et al*., 2019). In this study, high phenolic content can be found particularly in *S. dulcificum* flesh. Both flesh and seed of miracle fruit effectively improve glucose uptake based on the 2-NBDG uptake test.

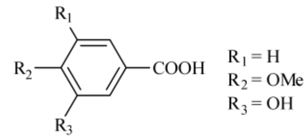
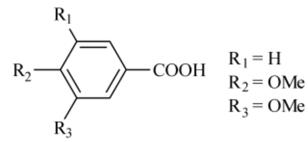
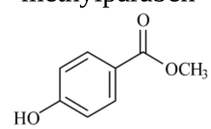
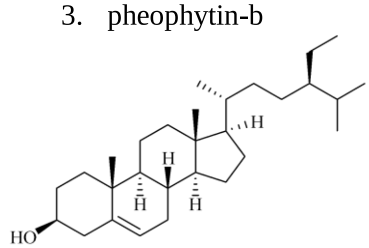
Anti-inflammatory activity

Inflammation is defined as a pathophysiological process distinguished by pain, edema, loss of function, redness and fever. Flavonoid that also known as nature's tender drugs have various pharmacological activities including anti-inflammatory activity. The ability of flavonoid to perform anti-inflammatory activity has been utilized in cosmetic industry and Chinese medicine field as a form of crude plant extracts since long ago. A variety of flavonoid molecule have been proven by many studies to have anti-inflammatory activity on various

Table No. 1
Compounds isolated from *Synsepalum dulcificum* (Schumach. & Thonn) Daniell.

Part of plant	Phytochemicals Present	Reference
Stem and root	• **Alkaloids:** 1. dihydro-feruloyl-5- methoxytyramine  2. N-cis-Caffeoyltyramine  3. N-cis-Feruloyl-tyramine  4. N-trans-Feruloyl-tyramine  5. 4-acetonyl-3,5-dimethoxy-p-quinol 	Wang *et al*., 2011 Ragasa *et al*., 2015 Mangla & Kohli, 2018
Stem	• **Lignan:** 1. (+)-syringaresinol 	Inglett & Chen, 2011 Wang *et al*., 2011 Ragasa *et al*., 2015 Mangla & Kohli, 2018
Part of plant	**Phytochemicals Present**	**Reference**

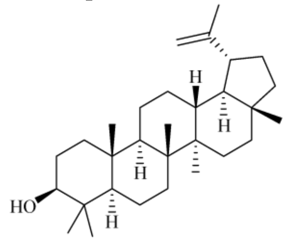
Stem	• **Lignan:** 2. (+)-syringaresinol  3. (+)-epi-syringaresinol 	
Stem and root	• **Phenolic acid:** 1. cis-p-coumaric acid  2. trans-p-coumaric acid  3. p-hydroxybenzoic acid  4. syringic acid  5. vanillic acid 	Wang *et al*., 2011 Ragasa *et al*., 2015 Mangla & Kohli, 2018
Part of plant	**Phytochemicals Present**	**Reference**

Part of plant	Phytochemicals Present	Reference
Stem and root	• **Phenolic acid:** 6. isovanillic  7. veratric acid  8. methylparaben 	
Fruit/ berry	• **Glycoprotein** 1. Miraculin • **Oil substance** 1. 4-hydroxy-2-oxetanone 2. Anthocyanins	Wang *et al*., 2011 Ragasa *et al*., 2015 Mangla & Kohli, 2018
Leaf	• **Phytosterols Triterpenes** 1. β-sitosterol and stigmasterol 2. pheophytin-a 3. pheophytin-b  4. lupeol 5. lupenone	Chen *et al*., 2010b Wang *et al*., 2011 Ragasa *et al*., 2015 Mangla & Kohli, 2018 Wang *et al*., 2020

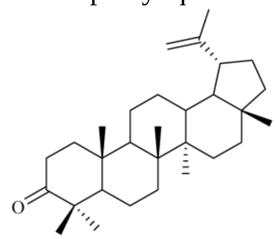
Leaf

- **Phytosterols Triterpenes**

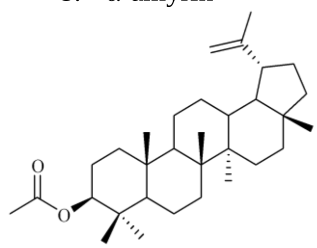
6. lupeol acetate



7. α-tocopheryl quinone



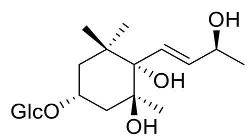
8. α-amyrin



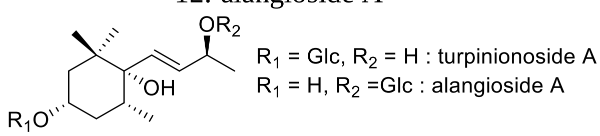
9. β-amyrin acetate

- **Apocarotenoids**

10. foliasalacioside K



11. turpinionoside A
12. alangioside A

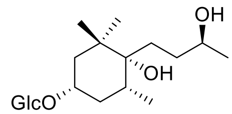


Part of plant	Phytochemicals Present	Reference

Leaf

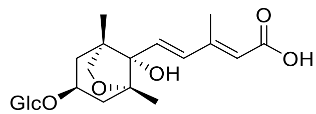
- **Apocarotenoids**

13. dihydrodendranthemoside A



- **Sesquiterpene glucoside**

14. dihydrophaseic acid 3’-O-β-D-glucopyranoside

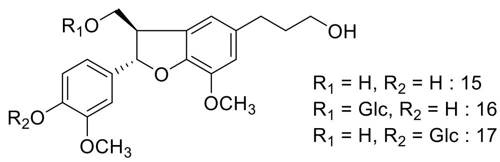


- **Lignans**

15. (7S, 8R)-dihydrodehydrodiconiferyl alcohol

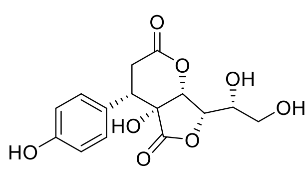
16. (7S, 8R)-dihydrodehydrodiconiferyl alcohol-9-b-D-glucopyranoside

17. (7S, 8R)-urolignoside



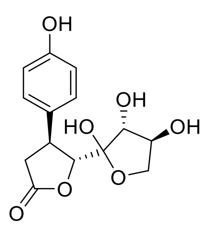
- **Phenyldilactone**

18. maysedilactone C



- **Phenolic**

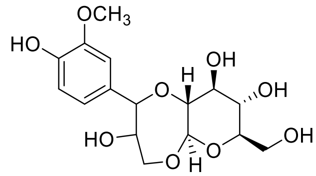
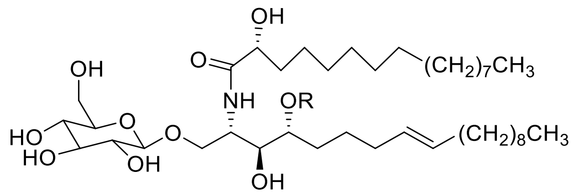
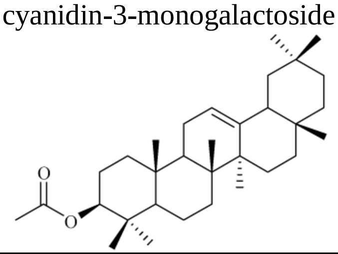
19. sawaranin

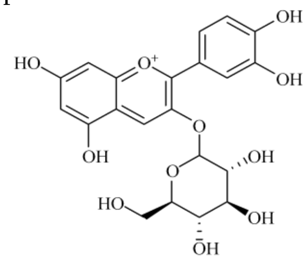
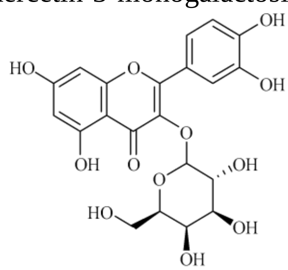
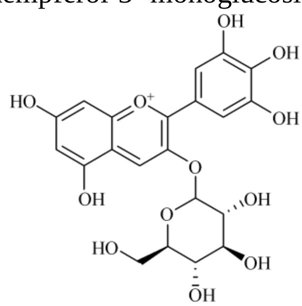


- **Alcohol**

20. syringin

Part of plant	Phytochemicals Present	Reference

Leaf	• **Propanoid** 21. junipetrioloside A  • **Flavonoids** 22. quercetin 23. quercetin-3-O-glucoside • **Cerebroside** 24. aralia cerebroside  • **Methyl glycoside** 25. methyl b-D-galactofuranoside • **Hydroxybenzoates** 26. methyl gallate	
Leaf and fruit	• **Colour pigment Flavonoids** 1. cyanidin-3-O-glucoside 2. cyanidin-3-monogalactoside 	Wang *et al*., 2011 Ragasa *et al*., 2015 Mangla & Kohli, 2018
Part of plant	**Phytochemicals Present**	**Reference**

Leaf and fruit	● **Colour pigment Flavonoids** 3. delphinidin-3- monoarabinoside  4. cyanidin-3-monoarabinoside 5. delphinidin-3-O- glucoside 6. quercetin-3-monogalactoside  7. kaempferol-3- monoglucoside  8. myricetin-3-monogatactoside

animal models of inflammation. Particularly, several flavonoids were found to inhibit chronic inflammation of some experimental animal models (Kim *et al*., 2004). In a study conducted by Osabor *et al*. (2016), *Synsepalum dulcificum* (Schumach. & Thonn) Daniell was found to contains several bio-active compounds include alkaloid 0.60% ± 0.2% from leaves extract, saponins 2.80% ± 0.2% from leaves extract; 0.62% ± 0.02% from root extract, flavonoids 2.40% ± 0.2% from leaves extract, polyphenols 3.52% ± 0.01% from leaves extract; 3.44% ± 0.01% from root extract, anthraquinones 0.02% ± 0.12% from root extract, cardiac glycosides 4.40% ± 0.20% from leaves extract; 4.20% ± 0.20% from root extract and tannins 4.00% ± 0.20% from leaves extract (Osabor *et al*., 2016). The molecular mechanisms of flavonoids involved in the anti-inflammatory activities include: activation of phase II antioxidant detoxifying enzymes, protein kinase C, nuclear factor-erythroid 2-related factor 2 and mitogen activated protein kinase (MAPK), inhibition of pro-inflammatory enzymes, such as lipoxygenase, inducible NO synthase and cyclooxygenase-2 and inhibition of NF-κB (Serafini *et al*., 2010). The NF-κB signaling pathway is a central common regulator for the action of inflammation. The compounds that inhibit different elements in the pathway are generally sought as possible therapeutics for inflammatory disorders and cancer (Yang *et al*., 2005). Cystic fibrosis is a genetic disease caused by insufficient or failure of the chloride channel cystic fibrosis conductance regulator (CFTR). It is categorized by severe lung inflammation and high amounts of the pro-inflammatory cytokine IL-8 in lung tissues (Fürst *et al*., 2017). Study shows that cardiac glycoside can effectively inhibit constitutive hypersecretion of the NF-κB-dependent pro-inflammatory cytokine IL-8 from cystic fibrosis lung epithelial cells (Yang *et al*., 2005). Other than being a critical part of the vascular system, endothelial cells also modulate the inflammatory process. For example, the extravasation of immune cells from the blood into the tissue. The inflammatory activation of endothelial cells can be decreased by cardiac glycosides.

Antioxidants activity

A study directed by Du *et al*. (2014), reported that *Synsepalum dulcificum* (Schumach. & Thonn) Daniell or miracle berry possessed antioxidant potential. This potential was analysed by using three methods namely DPPH (1,1-diphenyl-2-picrylhydrazyl), ABTS (2,2'-azino-bis (3-ethyl49 benzothiazoline-6-sulfonic acid)) as well as FRAP which was Ferric-Reducing Antioxidant Power. DPPH test showed that the flesh extract contained 96.3% of free radical scavenging potency and was greater than the seed extract which contained 54.3%, while ABTS test showed percentage of free radical scavenging action of flesh extract was 32.5%, and seed extract was 18.0%. Likewise, the flesh extract was greater than seed extract. Besides, the reduction capacity showed by FRAP test demonstrated that flesh extract contained 22.9 mmol/100 g of reduction capacity and was also significantly greater than the seed extract (5.2 mmol/100 g). The powerful decrease in aptitude of the flesh extract was due to the higher amount of phenolic content (1448.3 mg gallic acid equivalents/100 g fresh weight) and vitamin C (28.9 mg/100 g FW) (Du *et al*., 2014).

Another study performed by Chen *et al*. (2009) mentioned that *Synsepalum dulcificum* (Schumach. & Thonn) Daniell exhibited intermediate to high free radical scavenging potency. The finding of DPPH showed IC_{50} of methanol extract of plant's fruit was 73.5 ± 4.1 μg/mL while chloroform extract of miracle plant's pulp was 80.2 ± 3.4 μg/mL. The study suggested that antioxidant potential was conveyed by hydrogen in plant linked to radicals and formed stable radical. This process was subsequently ended the reaction of radical chain. Besides, another possibility was that the plant extract attached to ions of radical that needed for radical chain reaction and therefore the reaction was interrupted and ended. In addition, seeds 327.85 µmol Trolox/100 g FW of the fresh miracle fruits were found to have more antioxidant as compared to skin 269.62 ± 17.00 µmol Trolox/100 g FW and pulp 187.68 µmol Trolox/100 g FW. Whereas in dry condition, skin of miracle fruit contained antioxidant that was four times higher than the seeds and twice times greater than the pulp (He *et al*., 2016).

Moreover, antioxidant tested by DPPH test revealed that leaves of the *Synsepalum dulcificum* (Schumach. & Thonn) Daniell exhibited superior scavenging potential than seeds as IC_{50} of leaves was 0.06 mg/mL and IC_{50} of seeds was 5.3 mg/mL. Besides, ABTS (2,2′-azino-bis (3-ethylbenzo-thiazoline-6-sulfonic acid) also demonstrated that leaves of the plant were better radical scavenger than seeds. This reflected by IC_{50} amounts of 0.084 mg/mL (leaves) and 5.0 mg/mL (seeds). Similarly, hydroxyl radical scavenging activity also exposed than leaves showed better scavenging potency than seeds with IC_{50} of 0.18 mg/ml for leaves and 3.5 mg/mL for seeds. For Ferrous Ion Chelating activity (FIC), IC_{50} values were 0.083 mg/mL (leaves) and 1.9 mg/mL (seeds). This finding was too supported that leaves of miracle plant showed stronger scavenging activity than seeds. The ferric-reducing antioxidant power (FRAP) was also analyzed and expressed with absorbance at 700 nm. The leaves presented greater reducing power as compared to seeds. At the concentration of 0.00625 mg/mL, the ABS of leaves was 0.060. This value is comparable to absorbance of seeds at initial concentration of 0.625 mg/mL (Jian *et al*., 2017).

Furthermore, a study was carried out to verify that *Synsepalum dulcificum* (Schumach. & Thonn) Daniell leaves possessed antioxidant action. This action was checked by using Malondialdehyde (MDA), Superoxide Dismutase (SOD) and also Glutathione (GSH). MDA or oxidative stress marker was found not significantly different from normal control, glibenclamide and extract groups. The antioxidant property was reflected as in alloxan induced plus extracts treated groups, MDA was found lower than alloxan group (diabetic control). Besides, GSH values were also greater than alloxan group. Likewise, SOD values were higher in all groups except in alloxan induced group (Akinmoladun, 2016).

Babatunde *et al*. (2019), performed a study to analyze the antioxidant potential of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell. In the study, DPPH test revealed that miracle fruit seed oil displayed slightly higher in scavenging activity as compared to Carica papaya seeds oil probably due to polyunsaturated fatty acid present in the seeds of miracle berry. The highest antioxidant property of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell's seed oil was 60.05% at the concentration of 1 mg/mL. Similarly, Total Antioxidant Capacity (TAC) checked by using phosphomolybdate assay also revealed that oil of miracle fruit's seed was slight greater than *C. papaya* seed oil. Besides, antioxidant potency of seed oils intensified steadily as concentration increased. Thus, the study opined both oils were good edible oil with decent antioxidant potential to evade oxidative stress (Babatunde *et al*., 2019).

Cheng *et al*. (2015), stated that *Synsepalum dulcificum* (Schumach. & Thonn) Daniell exhibited powerful antioxidant activity. DPPH test in study showed that higher pH sodium acetate buffer (pH 6.0), 50% ethanol as well as 100% pure ethanol extract of miracle berry seed oil exhibited free radical scavenging percentage of more than 80%. pH 6.0 sodium acetate buffer and 50% ethanol displayed good scavenging percentage could be due to total phenolic content as when the concentration of oil was over 50%, total phenolic content started to drop. While 100% pure ethanol, good scavenging percentage could be due high amount of flavonoid content (3.1 μg/mg). For ABTS radical scavenging percentage, the finding was consistent with total phenolic content however no noticeable effect in pure ethanolic extract (100%). Next, FRAP test exposed that higher pH buffer possessed more ferrous ions chelating ability. Also, ethanolic extracts showed capacity to chelate Fe (II) with 100% pure ethanol displayed the best chelating power (Cheng *et al*., 2015).

Additionally, free, bound, and total antioxidant potentials of seeds, pulp and skin of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell were examined. Pulp as well as skin contained comparable free antioxidant action. Both were meaningfully more than free antioxidant in seeds. But obviously in the study, miracle fruit's pulp possessed low bound antioxidant because pulp structure made antioxidants in pulp difficult to bind. After all, skin of miracle fruit contained significantly higher of total antioxidants (27.15 μmol/g) as compared to seeds (16.94 μmol/g) and pulp (19.88 μmol/g). Seeds (16.94 μmol/g) recorded the lowest antioxidants among three tested components. However, free antioxidant activity that the seed contributed was 49%, bound antioxidant activity was 76% and total antioxidant activity was 58% (Inglett & Chen, 2011).

Tajudeen Olabisi Obafemi *et al*. (2017b), conveyed that methanol extract of miracle plant leaves exhibited antioxidant action. In the study, DPPH test revealed inhibition of radical was dose dependently. At the greatest tested concentration (400 μg/mL), the scavenging activity was the highest which was about 93.53%. Besides, ABTS test showed there were outstanding inhibition percentage against ABTS radical at the concentration of 200 μg/mL (85.29%) and 400 μg/ml (87.99%). While in nitric oxide scavenging activity, the inhibition percentage was excellent and in dose dependent order. The maximum inhibition percentage of free radical (69.42%) was at the highest tested concentration (400 μg/mL). Meanwhile the iron-chelating ability of methanol extract displayed noticeable activity in chelation although the standard (EDTA) used in the study showed better chelation potency. At highest tested concentration 400 μg/ml, iron chelating activity percentage of methanol extract was 48.86% and 60.52% for EDTA. Next, miracle leaves extract displayed noticeably reducing power. It presented absorbance values of 1.21 while the standard (quercetin) showed absorbance values of 1.80. For hydroxyl radical scavenging action, the methanol extract showed dose dependently high scavenging action when compared to standard (mannitol) used. At 400 μg/mL concentration, inhibition percentage of hydroxyl radical of methanolic extract was 79.86% whereas mannitol was 80.56%. Subsequently, methanol extract was also capable to inhibit lipid peroxidation moderately. It displayed dose dependent manner in inhibition of lipid peroxidation when compared to ascorbic acid that used as standard in the study. At the greatest tested concentration, the inhibition percentage was 48.79% for the extract and 74.65% for the standard (Obafemi *et al*., 2017b).

Study by Han *et al*. (2019), revealed that *S. dulcificum* has high phenolic content and antioxidant capacity. Liu *et al*. (2017), also claimed that miracle plant's leaves displayed antioxidant potential. The DPPH test was checked by using several extraction temperatures which ranged from 40 to 80°C. Initially, the scavenging ability of 70% methanol extract increased steadily with the maximum scavenging activity at 60°C, then it declined until the temperature of 80°C. This because high temperature may decompose the antioxidants in the extract. The 70% methanol extract was also tested by using different extraction times. The percentage of scavenging activity started to increase at the time of 0.5 hours to 3 hours, then it began to decline after more than 3 hours of extraction time. The reason was similar; the antioxidant may be decomposed at lengthy extraction time. Besides, dried miracle plant's leaves were mixed with different methanol concentrations (50, 60, 70, 80, and 90%) and reflux at 70°C for three hours. 50 to 70% of methanol concentrations showed escalation in scavenging activity with 70% showed the highest activity but then again it declined after

70% concentration. This because antioxidant leakage happened in greater concentration and therefore decreasing the scavenging activity. Next, 70% methanol, three hours' extraction time with 70°C of extraction temperature was fixed to test different ratios of methanol solution to leaves mass on scavenging ability. The various ratios analyzed in this test were 50:1, 75:1, 100:1, 150:1 and 200:1. Typically, according to Bey *et al*. (2013), a lower solution to leaves mass ratio will lead to partial extraction while higher solution to leaves mass ratio will give more dissolved oxygen and allow oxidation of antioxidant to take place. From this test, the greatest scavenging action was clearly displayed at the ratio of 100:1. In short, optimization circumstances for DPPH scavenging ability were 3 hours extraction time, 60°C extraction temperature, 70% methanol solution, and methanol solution to leaves ratio of 100:1 (Liu *et al*., 2017).

Anticancer activity

Cancer is the result of a combination of genetic and non-genetic changes brought upon by environmental factors that trigger undesirable activation or inactivation of specific genes leading to neoplastic transformations of the normal cells or abnormal cell growth (Chakraborty & Rahman, 2012). In description, cancer refers to a group of diseases that take place when malignant forms of abnormal cell growth develop in one or more body organs. It is a product of genetic mutations, which can continue its division phase and grow to create more tumors, invade neighboring tissues and even spread to other parts of the body.

One unique characteristic of cancer is that it can develop at any stage in life whether during childhood, adolescence or senior stage and in any body organ. Statistics show that more than 1 million new cases of cancer were diagnosed in the United States in 2016, with the figure standing at 1685210. In the female category, breast, lung and bronchus, colorectal, uterine and thyroid cancer were the most common diagnoses. In the male category, prostate, lung and bronchus, colorectal, bladder and melanoma were the most common diagnoses (Arem & Loftfield, 2018).

There are certain risk factors that can increase the likelihood of cancer disease in humans, such as carcinogens and lifestyle or environment-related factors. Carcinogens are substances that can cause cancer in living cells and are classified into genotoxic and non-genotoxic groups. Genotoxic carcinogen denotes a kind of chemical that cause cancer by directly altering the genetic material of target cells, while non-genotoxic carcinogen describes another kind of chemical that cause cancer unrelated to gene damage via indirect means (Hayashi, 1992; Dieter, 2018). Other types of carcinogens include chemical carcinogens (benzo[a]pyrene, asbestos), physical carcinogens (UV radiation, X-rays), and biological carcinogens (viruses such as HPV, bacteria) (Bukhtoyarov & Samarin, 2015). Carcinogens found in food include sodium nitrite, which is a common coloring substance in meat, arsenic in drinking water and benzene contamination in food (Lachenmeier, 2009).

On the other hand, certain lifestyle factors that contribute to chances of cancer are diet, alcohol consumption, tobacco smoking and energy balance (Ames *et al*., 1995; Irigaray *et al*., 2007; Wei *et al*., 2010). In terms of prevention, there are multiple approaches for the prevention of cancer, such as the inclusion of harm reduction (reducing exposure to known causes of cancer), clinical interventions (vaccines, chemoprevention), and health promotion (promoting behaviors that reduce cancer likelihood) (White *et al*., 2013). Certain lifestyle changes that aid cancer prevention involves a balanced diet with major intakes of vegetables and fruits and a reduction in fatty, oily and processed foods, moderation in alcohol consumption, reduction in tobacco smoking for smokers or tobacco cessation and an increase in time spent on physical exercise.

In terms of clinical intervention, early detection and diagnosis, prognosis and treatment will help in impeding the progression of cancer to more advanced stages or other parts of the body. Treatment options for cancer depends on the stage of progression, purpose, risks, costs, complications and finally, the type of cancer. Common choices are surgery for tumors, radiotherapy and chemotherapy (Arruebo *et al*., 2011).

Furthermore, drugs are also available as part of the treatment scope. These drugs are categorized as alkylating agents, antimetabolites, anthracyclines, mitotic inhibitors and hormone chemotherapeutic drugs (Abbas & Rehman, 2018). Alkylating agents are classic anticancer drugs which comprise of nitrogen mustards such as chlorambucil, nitrosoureas and busulfan (Blagosklonny, 2005; Falzone *et al*., 2018). Antimetabolites incorporate folate analogs e.g. methotrexate and pyrimidine analogs e.g. fluorouracil. Anthracyclines make up doxorubicin and mitotic inhibitors encompasses vinca alkaloids e.g. vinblastine, vincristine. Nano-medicine is a recently discovered area of therapy for precision medicine e.g. doxorubicin, its release is controlled by temperature via a liposomal formulation, ThermoDox (Pucci *et al*., 2019). Study by Afzal *et al*. (2021), revealed that the ethanol fruit extract of *S. dulcificum* has potent anticancer activities which useful to be use against colorectal cancer.

A study was conducted to evaluate any potential anticancer activities of the ever-green shrub, *Synsepalum dulcificum* (Schumach. & Thonn) Daniell. It was to assess the cytotoxicity of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell on human colon cancer (HCT-116 and HT-29), human monocytic leukemia (THP-1) and normal (HDFn) cell line. To begin, *Synsepalum dulcificum (Schumach. & Thonn) Daniell* shrubs were obtained from the Agri-Aqua Network International in Philippines. Next, HCT-116 and HT-29 human colorectal cancer cells, and THP-1 human monocytic leukaemia cells were previously procured from the American Type Culture Collection, while HDFn human neonatal dermal fibroblasts were previously procured from Invitrogen. HCT-116, HT-29, and HDFn were cultured to 90% confluency in Dulbecco's Modified Eagle Medium (DMEM) with 10% fetal bovine serum and 1 x antimycotic antibiotic in 50 mL T-flasks at 37°C in 95% humidity and 5% CO_2 atmosphere. THP-1 was cultured to 90% confluence in Roswell Park Memorial Institute medium with the same supplements and conditions as above. All cells were harvested via 0.05% trypsin-EDTA in phosphate buffered saline at pH 7.4. All cells were harvested at their log phase (Seong *et al*., 2018).

The next step continued with *Synsepalum dulcificum* (Schumach. & Thonn) Daniell extraction by harvest of its leaves, stems and berries, which was then cleaned with tap water and later rinsed twice in sterile distilled water. After cleaning, the materials were left to dry for 1 week at room temperature. The next procedure followed by the mixture of 10 g of each powdered sample with 100 mL of freshly prepared 80% MeOH and 10% EtOH solvent for 24 hours with a magnetic stirrer. The mixtures went through a centrifugation process at 4500 RPM for 10 minutes, in which the solvent was collected in respective flasks. An additional 100 mL of freshly prepared solvents were added to the residues, with the same procedure repeated again for extraction. The two collected solvent layers were combined accordingly and underwent evaporation via a rotary evaporator. Later on, the products from it were lyophilized at -40°C to obtain dried extracts. The final step involved the dilution of the dried extracts with 0.2% DMSO (dimethyl sulfoxide) in phosphate buffered saline to the concentration of 1 g/mL (Seong *et al*., 2018).

Antihyperuricemic activity

Hyperuricemia is the consequence of augmented creation of uric acid and diminished excretion of uric acid (Zhao *et al*., 2015). Miracle berry was found to have ability to lower uric acid through xanthine oxidase inhibition (Shi *et al*., 2016). This is because xanthine oxidase forms uric acid by catalyzing hypoxanthine and oxidation of xanthine. Thus, in order to impede the biosynthesis of uric acid and treat hyperuricemia, the agent that can inhibit xanthine oxidase is needed (Unno *et al*., 2004). According to Shi *et al*. (2016), powder of miracle fruit was extracted by using butanol and was then partitioned with water, butanol, hexane and ethyl acetate. They were checked for inhibition of xanthine oxidase in vitro and finding demonstrated that fraction of ethyl acetate showed the greatest inhibition. Besides, water extract of miracle fruit exhibited xanthine oxidase suppression dose dependently. At the concentration of 500 µg/mL, water extract impeded xanthine oxidase noticeably in monosodium urate treated RAW264.7 macrophages which greater than 100 µg/mL allopurinol (Shi *et al*., 2016).

In the same study, anti-hyperuricemia effect was tested by using mice treated *in vivo* with 250 mg/kg/day oxonic acid potassium salt. The experimental animals were treated with low dose (500 mg/kg/day), high dose (1000 mg/kg/day) of butanol extract of *S. dulcificum* as well as positive control named 10 mg/kg/day of allopurinol. Then, result demonstrated that the extract did not exert side effects in organs as no substantial difference in the weights liver and kidneys. Additionally, the extract also showed no toxic effects since it did not amend the level of blood urea nitrogen (BUN) as well as serum creatinine level. Also, high dose butanol extract was able to lessen the augmented hepatic xanthine oxidase and reduced level of serum uric acid triggered by oxonic acid potassium salt. These discoveries proposed that the effect of high dose butanol extract was similar to allopurinol (Shi *et al*., 2016). Furthermore, another study performed by Lin *et al*. (2018), exposed that ethanol extract and also water extracts of miracle plant's leaves can attenuate serum uric acid without exhibiting adverse effect to the experimental animals. In the study, ethanol extract was more effective effect than water extract of miracle leaves. It meaningfully augmented the serum creatinine and lessened the blood urea nitrogen of oxonate-treated rat. The declining effect of uric acid level was due to the presence of quercetin-3-O-α-L-rhamnopyranoside 1.74 g/100 g, hyperoside 0.77 g/100 g and quercetin 0.17 g/100 g (Lin *et al*., 2018).

Anticonvulsant activity

Synsepalum dulcificum (Schumach. & Thonn) Daniell possessed anticonvulsant properties according to a study performed by Jeremiah *et al*. (2015a). Seizure is an episode of abnormal electrical events in brain that leads to the change in behavioral and physical findings (Krumholz *et al*., 2007). The result showed that aqueous fraction of miracle plant's seeds cannot defend experimental animal against pentylenetetrazole (PTZ) induced seizure, but it showed some mortality protection. According to Huang *et al*. (2001), PTZ is GABAA receptor's non-competitive antagonist, and it binds to receptor's picrotoxin (PTX). The result proposed that extract showed slight affinity toward picrotoxin (PTX) of gamma-aminobutyric acid type A (GABAA), subsequently triggered some level of neurotransmission inhibition and exhibited some mortality protection percentage.

In addition, aqueous extract had no effect on seizure onset also cannot protect the animal against strychnine-induced convulsion. The extract displayed 33.3% mortality protection whereas diazepam 5 mg/kg which acted as reference drug gave 66.67% protection against mortality (Jeremiah *et al*., 2015a). Strychnine is glycine antagonist while glycine is significant central nervous system (CNS)'s inhibitory neurotransmitter (Carmans *et al*., 2010; Brams *et al*., 2011). The finding suggested that extract composed of component that might have glycine receptor affinity or the component might exert inhibitory neurotransmission and thus offsetting strychnine's excitatory effect (Jeremiah *et al*., 2015a). While the minor protective effect in extract might be due to the antioxidant action in the seeds (Inglett & Chen, 2011). This is because commencement of epilepsy has been related to oxidative stress and free radicals may implicate in epilepsy (Sudha *et al*., 2001). Therefore, the doses of aqueous fraction administered to mice might have potency to lessen the oxidative stress (Jeremiah *et al*., 2015a).

Furthermore, maximal electroshock (MES)-induced seizure in mice showed doses 0.3, 0.6 and 1.2 mg/kg used in experiment were not successfully prevented the animals against tonic hind-limb extension. But recovery time reduced dose dependently with doses of 0.6 and 1.2 mg/kg showing substantial recovery time reduction in comparison to saline control. This presented that the aqueous fraction of seed extract of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell exhibited anticonvulsant properties (Jeremiah *et al*., 2015a). The summarized pharmacological potential/activities of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell are presented in Table No. 2.

Table No. 2
The pharmacological activities of *Synsepalum dulcificum* (Schumach. & Thonn) Daniell.

Pharmacological Properties	Part of Plant	Extract/Fraction	Dose/Amount Used	Experimental animal/cell line culture	Outcome	Conclusion	Reference
Antidiabetic	Fruit and leaves	Aqueous and ethanol extract	50% of fruit extract, 50% of leaf extract, 100% of fruit extract and 100% of leaf extract	Alloxan-induced male albino rats	The administration of *S. dulcificum* extract decrease the blood glucose level of alloxan-induced male albino rats.	*S. dulcificum* extract has significant effect on blood glucose level.	Dioso *et al*., 2016
	Leaves	Methanol extract	30 and 60 mg/kg BW	Wistar albino rats	The *S. dulcificum* extract decrease the serum glucose level in animal model.	There are significant positive effect of *S. dulcificum* extract on antidiabetic activity.	Obafemi *et al*., 2017a

	Pulp, seed and leaves	Aqueous and ethanol extract	1.25, 2.5, 5, 10, and 20 mg/mL	*In vitro*, porcine pancreatic α-amylase	*S. dulcificum* extract has higher inhibition of α-amylase and α-glucosidase activity.	*S. dulcificum* pulp extract has better antidiabetic effect compared to its seed and leaves	Fazilah *et al.*, 2020
Antimicrobial	Leaves	Methanol and ethanol extract	-	*Listeria monocytogenes*	Both *S. dulcificum* extract has smaller antimicrobial activity against *L. monocytogenes*	Minimal antimicrobial activity against *L. monocytogenes* can concluded in the *S. dulcificum* extract.	Wasoh *et al.*, 2018
	Seeds and leaves	Sodium hydroxide (NaOH extract)	- 0.1 g of powdered sample (Seeds and leaves) in 10 mL of 0.1 M NaOH.	*Pseudomonas aeruginosa, Klebsiella granulomatis, Aspergillus fumigatus, A. flavus and A. niger*	*S. dulcificum* extract has significant positive effect toward antimicrobial effects against *P. aeruginosa* and *K. granulomatis.*	The microbial activity of *P. aeruginosa* and *K. granulomatis* can be inhibit by *S. dulcificum* extract.	Lateef *et al.*, 2016
	Leaves	Aqueous extract	4 mg/mL, 8 mg/mL, 16 mg/mL and 32 mg/mL	*Streptococcus mutans, Streptococcus sobrinus* and *Lactobacillus salivarius.*	The microbial activity of *S. dulcificum* can be seen against *S. mutans* and *S. sobrinus***.**	The activity of *S. mutans* and *S. sobrinus* can be inhibit by *S. dulcificum*.	Ibrahim *et al.*, 2020.
	Fruit	Petroleum ether extract and ethanol extract	100 g	*Staphylococcus aureus, Bacillus subtilis, Proteus vulgaris, Pseudomonas aeruginosa, Klebsiella pneumonia,* and *Escherichia coli.*	There are significant antimicrobial effect of *S. dulcificum* against all six bacterial strains.	The inhibition zone of *S. dulcificum* ethanol extract is better than petroleum extract.	Afzal *et al.*, 2021

Antioxidant	Flesh and seed	Methanol extract	20 g	DPPH, ABTS and FRAP	Antioxidant activity of *S. dulcificum* flesh has higher effect than seed.	*S. dulcificum* has significant effect on antioxidant activity.	Du *et al*., 2014
	Fruit and pulp	Methanol and chloroform extract	-	DPPH	*S. dulcificum* has positive effect on reducing lipid oxidation.	Antioxidant effect can be found in *S. dulcificum* leaves extract.	Chen *et al*., 2009
	Skin, pulp and seed	80% aqueous methanol extract	4 g	DPPH	*S. dulcificum* skin has high antioxidant content compared to pulp and seeds.	*S. dulcificum* has positive effect on antioxidant activity.	He *et al*., 2016
	Fruit and seed	Ethanol extract		C2C12	*S. dulcificum* fruit extract produced phenolic content and antioxidant capacity than seed.	*S. dulcificum* has positive effect on antioxidant activity.	Han *et al*., 2019
Antioxidant	Seeds and leaves	80% ethanol extract	Seeds: 0.625, 1.25, 5, 10, 20, 40 and 80 mg/mL Leaves: 0.00625, 0.0125, 0.025, 0.05, 0.1, 0.2, 0.4 and 0.8 mg/mL	DPPH, ABTS, hydroxyl radical scavenging activity, FIC and FRAP	Ferrous Ion Chelating (FIC) related to the antioxidant activity, which it shows that significant increase in FIC activities.	*Synsepalum dulcificum* (Schumach. & Thonn) Daniell extract has significant effect on the antioxidant activity.	Jian *et al*., 2017
	Seeds	Hexane extract	0.2, 0.4, 0.6, 0.8 and 1 mg/ml	DPPH and Phosphomolybdate assay	Free radical scavenging ability can be found in the *Synsepalum dulcificum* seed	*Synsepalum dulcificum* has good antioxidant activity	Babatunde *et al*., 2019
Anticancer	Stem and berry	80% methanol and 10% ethanol extract	200 μg/ml	HCT-116, HT-29 human colorectal cells	*S. dulcificum* stem and berry extract has positive anticancer properties against HCT-116 and HT-29 human colorectal cells.	*S. dulcificum* stem and berry extract has the anticancer properties.	Seong *et al*., 2018

	Fruit	Petroleum ether extract and ethanol extract	2g	Colorectal cells (HCT-116 and PCE cell)	The ethanol extract of *S. dulcificum* produced potent anticancer activity.	*S. dulcificum* has significantly positive effect of anticancer against colorectal cancer.	Afzal *et al*., 2021.
Anti-hyperuricemia	Fruit	Water, butanol, hexane and ethyl acetate fraction	1, 2.5, 5, 7.5 and 10 mg/ml	RAW264.7 macrophages and Male (Institute of Cancer Research) ICR mice	*S. dulcificum* extract has ability to inhibit the xanthine oxidase activity.	Significant positive effect can be seen on antihyperuricemia activity on *S. dulcificum* extract.	Shi *et al*., 2016
Anti-convulsion	Seed	Aqueous fraction of methanol	0.3, 0.6 and 1.2 mg/kg	Albino mice	*Synsepalum dulcificum (Schumach. & Thonn) Daniell*extract provided protection gainst the mortality due to convulsion.	There is significant anti-convulsant effect of *Synsepalum dulcificum (Schumach. & Thonn) Daniell*extract.	Jeremiah *et al*., 2015a

Significance of Synsepalum dulcificum (Schumach. & Thonn) Daniell as food supplement

The plant kingdom stands out because it plays a significant portion of the human diet. *Synsepalum dulcificum*, also called the miracle fruit, which has the unique taste-modifying property can cause sour food to taste sweet while it is tasteless due to the presence of miraculin in the fruit. The edible pulp of the small, ellipsoid, bright red berry-like fruits of this plant which possess this extraordinary property of altering flavors on taste buds from acidic tastes to sweet could be exploited for use in food industries as it is a potential source of natural, non-caloric sweetener for use in food. As the expanding number of people suffering from chronic diseases linked to high sugar consumption, it driven up the demand for natural, non-caloric sweeteners like miraculin (Demesyeux *et al*., 2020). Besides, miracle fruit was used by some Western African tribes to flavour beer and improve the palatability of sour foods (Swamy *et al*., 2014). For decades, local people in West Africa have been interested in the plant's potential uses, and the fruit has been used to sweeten sour meals and beverages such as Koko and Kenkey, made from fermented maize and millet, and palm wine (Akinmoladun *et al*., 2020).

Apart from miraculin, other pharmacologically active compounds like polyphenolic compounds and flavonoids have been isolated from the fruits. These antioxidants have found to have effect in showing the inhibition activity of inflammation and oxidatice stress. The plant has also been credited with notable nutritional benefits which can improve the quality and nutritional value of food. As the future trend moves toward the development of functional food with specific health effects, scientists, food manufacturers, and consumers are becoming more aware of the importance of antioxidant constituents of plant materials in the maintenance of health and protection from chronic diseases such as coronary heart disease and cancer (He *et al*., 2016). According to Shi *et al*., (2016), the findings imply that miracle fruit could be an effective treatment for acute gouty arthritis and could be developed as a health food (Shi *et al*., 2016).

Furthermore**,** due to the presence of the pigment components of miracle fruits such as anthocyanin, it has shown to improve human health and reduce illness risk. In addition, anthocyanin-containing phenolic compounds, which can be found in fruits, leaves, flowers, vegetables, nuts, seeds, and barks, constitute an important element of the human diet and are also used as medical treatments (He *et al*., 2016).

Moreover, due to the formation of an orange-red colour when added to carbonated water and sugar solutions, miracle fruit was examined as a potential food colourant (Swamy *et al*., 2014). Besides, the bright red colour of the skin, which is mostly attributable to cyanidin3-monoglycosides, also shown that it may make it useful as a food and beverage colourant (Buckmire & Francis, 1978). The FDA's acceptance of the miracle fruit as an ingredient paved the way for more research into the fruit (Swamy *et al*., 2014).

Study of plant with probable medicinal properties are becoming more fascinating lately. In the present review, we have critically analyzed the current evidence on the traditional uses, chemical profiles, and pharmacological potential and clinical trials of *Synsepalum dulcificum*. The higher pharmacological characteristics, e.g., antioxidant, analgesic, anticancer, dysgeusia, antioxidant, antidiabetic and anti-inflammatory, linked to this plant recommend its exploitation in nutraceutics, medicines, and pharmaceutics this review. Henceforth, we corroborated that *Synsepalum dulcificum* (Schumach & Thonn) Daniell could be investigated as a potential source of higher added value compounds for the pathological ailments as pharmacological compounds. However, in some aspects of study, the data acquired is still very imperfect, thus future research is hopeful to discover the precise mechanism of action of bioactive components in *Synsepalum dulcificum* (Schumach & Thonn) Daniell extract. Besides, further studies needed to explore the chemical constituents and their nutraceutical, toxicological profile and clinical uses of this multipurpose plant in cosmetic industry as well as to employ its valuable effects on human beings.

CONCLUSIONS

Study of plant with probable medicinal properties are becoming more fascinating lately. In the present review, we have critically analyzed the current evidence on the traditional uses, chemical profiles, and pharmacological potential and clinical trials of Synsepalum dulcificum. The higher pharmacological characteristics, e.g., antioxidant, analgesic, anticancer, dysgeusia, antioxidant, antidiabetic and anti-inflammatory, linked to this plant recommend its exploitation in nutraceutics, medicines, and pharmaceutics this review. Henceforth, we corroborated that *Synsepalum dulcificum* (Schumach. & Thonn) Daniellcould be investigated as a potential source of higher added value compounds for the pathological ailments as pharmacological compounds. However, in some aspects of study, the data acquired is still very imperfect, thus future research is hopeful to discover the precise mechanism of action of bioactive components in *Synsepalum dulcificum* (Schumach. & Thonn) Daniellextract. Besides, further studies needed to explore the chemical constituents and their nutraceutical, toxicological profile and clinical uses of this multipurpose plant in cosmetic industry as well to employ its valuable effects on human beings.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

FUNDING

This work was supported through the Annual Funding track by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia (Project No. GRANT 5,998).

ACKNOWLEDGMENTS

This work was supported by the Deanship of Scientific Research, Vice Presidency for Graduate Studies and Scientific Research, King Faisal University, Saudi Arabia under Annual Research Track (Grant No. GRANT 5,998).

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