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Phytochemical Profile and Pharmacological Potential of *Solanum dubium* (Fresen.)

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ABSTRACT: *Solanum dubium* Fresen. is a species of the Solanaceae family. It is an indigenous wild plant of Sudan and other East African countries. The aim of this review is to explore and analyze its phytochemical constituents and pharmacological activities. The review followed the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) 2020 checklist guidelines. The study involved searching in reputable electronic databases, such as PubMed, ScienceDirect, and Google Scholar. Only 21 articles were deemed eligible for inclusion in this review. Phytochemical groups are abundant in Solanaceae family and *Solanum* species, demonstrating various pharmacological properties. Few published studies (n = 6) have focused on isolation and identification of compounds, mainly from the seeds, while secondarily from aerial parts, whole plant, and leaves. Further investigations of the phytochemical composition of all organs are recommended due to the presence of alkaloids, sterols, and coumarins. In addition, few articles have focused (n = 17) on pharmacological properties, including antioxidant and antimicrobial activities. All pharmacological studies have focused on the seeds, fruits, whole plant, aerial parts, and leaves. The plant shows significant antioxidant activity, which helps in discovering the molecules used for treating many related oxidative stress diseases. Regarding cytotoxic activity, the plant has been only examined, *in vitro*, by using hepatic, lung and renal cell lines. Additional research is recommended for other pharmacological properties, focusing on all plant organs. Moreover, research is required for anticancer properties as well as other related oxidative stress diseases by using various cell lines *in vivo* and clinical validations.

1. INTRODUCTION

It is widely recognized that medicinal plants provide humans with unique and complex chemical compounds in abundance. These natural compounds are unlikely to be targeted in synthetic drug development programs; notable examples include

vinblastine, vincristine, taxol, d-tubocurarine, and digoxin (Fabricant and Farnsworth, 2001). These plants play a crucial role in pharmacy and pharmacology because of their extensive range of bioactive compounds, such as alkaloids, flavonoids, glycosides, and terpenoids, exhibiting significant pharmacological activities, such as anti-inflammatory, antimicrobial, and

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anticancer effects. Many of these compounds serve as templates and guides for drug development. For instance, artemisinin, an antimalarial agent derived from the Sweet Wormwood plant (*Artemisia annua*), and paclitaxel (*Taxol*), an anticancer agent, derived from the Pacific Yew tree (*Taxus brevifolia*), are prime examples of how natural products have revolutionized modern medicine (Newman and Cragg, 2016).

Solanum dubium Fresen. (Syn: *Solanum coagulans* Forssk.) is a species of the Solanaceae family, and is locally known as *El-Gubbain*. It is a wild plant native and indigenous of Sudan and other East African countries (Figure 1). The plant is also located in the nearby countries, such as Saudi Arabia and Yemen; it is also found in China (Ahmed et al., 2009; Ghaleb Dailah, 2022; Mohamed, et al., 2016a; Zhang, 2015). It flourishes primarily in Khartoum State during the rainy season and is commonly found along both the western and eastern banks of the river White Nile. This species also extends south of the Blue Nile and is widely distributed across the regions, such as Gezira, Kordofan, and Darfur (Mohamed, et al., 2016a).

Solanum dubium is a woody herb (Figure 2), grows up to 30 cm height, with a sturdy, upright green stem bearing sharp spines near the base. The alternate leaves are simple and ovate, and range from acuminate to obtuse at the tip, with a pale green-brown hue. The rootlets are brown, with the main root reaching approximately 5 mm in thickness and 15 cm in length. The plant's hermaphroditic, actinomorphic flowers feature a yellow, core-like center. Its spherical berries, about 1 cm in diameter, have a smooth, glossy surface;

they are initially green and enclosed in a spiny calyx, turning yellow when mature. Clusters of fruit grow on one side of the stem, and the seeds are dark brown with a finely pitted surface (Ahmed et al., 2009). A cross-section of *Solanum dubium* stem displays a circular arrangement with an outer cork layer, followed by a cortex and a central woody area encircled by the phloem; the cork layer consists of 5–6 layers of yellowish-brown, rectangular, lignified parenchyma cells. Below this, the cortex is a broad zone of thin-walled, elongated cells containing starch grains and sandy crystals, with scattered sclerenchyma fibers, stone cells, and sclereids. The narrow phloem layer, adjacent to the cortex, consists of irregularly positioned parenchyma cells, sieve tubes, and fibers. The medullary rays are uni- to bi-seriate, which extend from the phloem into the cortex, containing thin-walled cells with starch grains. The wood forms the largest section, with groups of vessels, thick-walled parenchyma, fibers, and xylem parenchyma, all embedded with starch grains (Patel et al., 2018).

The plant has several traditional applications among Sudanese communities. Nomadic groups use its fruit to ferment warm milk. Additionally, a mixture of water and ground powder of *S. dubium* is applied to separate hair from animal hides (Mohamed Ahmed et al., 2009). Traditionally, the plant is also used to relieve asthmatic attacks, as it is customarily utilized as a therapy to relieve asthma among local populations in Sudan. Some reports describe of combining its seeds with honey to aid in healing skin injuries and wounds (Mohamed et al., 2016b; Mohamed Ahmed et al., 2009).



Figure 1. The geographical global distribution of *Solanum dubium*. (Downloaded from: www.gbif.org in November 2024).

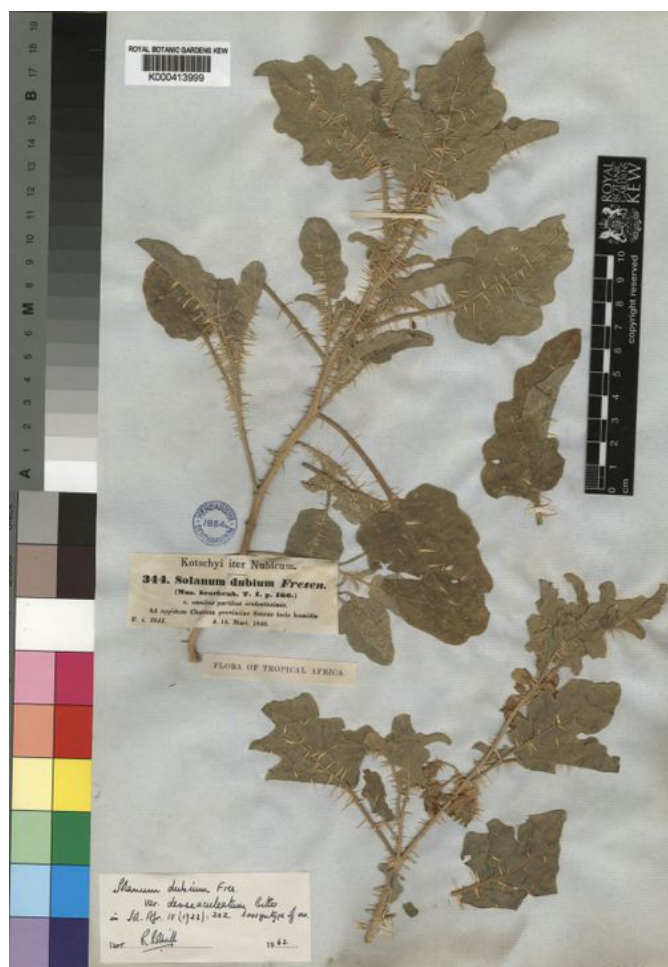


Figure 2. The aerial morphological part of *Solanum dubium*. (Downloaded from www.gbif.org in November 2024.)

Moreover, especially in some parts of Western Sudan, the raw seeds are swallowed for treating abdominal pain (Muhakr et al., 2024). Additionally, in another area (South Kordofan), a decoction of the roots is used in treatment of jaundice (Issa et al., 2018). In addition, the plant is applied as a dressing on the wounds and skin tumors (Muddathir et al., 2017). In Djibouti (Somali peninsula), traditional healers use paste of the topical leaves of *S. coagulans* in alleviating tooth decays (Hassan-Abdallah et al., 2013). In China, the aerial parts are used traditionally in alleviating symptoms of edema, toothache, and rheumatic arthritis (Qin et al., 2016). In addition, the seeds and roots of *S. coagulans* are traditionally used for treating cough (Ghaleb Dailah, 2022).

The aim of this review is to explore and analyze the phytochemical constituents and pharmacological activities of *Solanum dubium* (Fresen.). We observed that ethnopharmacological research of this plant is limited, particularly concerning its isolated phytochemical compounds and pharmacological uses, compared to other members of the Solanaceae family, especially species within the Solanum genus.

2. METHODOLOGY

This review was conducted to explore the relatively under-researched plant *S. dubium* in the fields of ethnopharmacology and bioassay-guided fractionation, isolation, and characterization of active constituents. The plant has significant and diverse traditional uses. The methodology adheres to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 checklist guidelines (Page et al., 2021). This study involved searching several reputable electronic databases, such as PubMed, ScienceDirect, and Google Scholar. The keywords used included the following combination: “*Solanum dubium*,” “*Solanum coagulans*,” “phytoconstituents of *Solanum dubium*,” “phytoconstituents of *Solanum coagulans*,” “pharmacological uses of *Solanum dubium*,” and “pharmacological uses of *Solanum coagulans*.” Boolean operators were employed, where applicable, to broaden the search. Additionally, the reference lists of selected articles were examined for relevant studies. Studies were included if they were published in English and covered all years. All studies characterizing the phytochemicals and those focusing on the pharmacological properties of *S. dubium* and *Solanum coagulans* were considered. *In vivo*, *in vitro*, animal, and human studies were also included. However, studies focusing on other Solanaceous species were excluded, as were any topics related to *S. dubium* and *S. coagulans* that were not relevant to phytochemical constituents and pharmacological uses. The study selection was conducted based on titles, abstracts, and full-text reviews wherever access was granted. The data were synthesized qualitatively; six authors independently collected the data based on the results of selected successive electronic databases; they then convened to review and summarize the relevant topics. Subsequently, four additional authors evaluated the first draft by conducting an independent search, and their comments were incorporated into the final document. This combination of teamwork ensured that any risk of bias in collecting and analyzing the data, in accordance with our specified objectives, was minimized and avoided. This review acknowledged its limitations, citing the lack of extensive research published on *S. dubium*.

3. RESULTS

3.1. Study selection

The PRISMA flow chart, in accordance with the PRISMA 2020 checklist guidelines (Page et al., 2021) was utilized (Figure 3). A total of 927 papers were identified from the following databases: PubMed, ScienceDirect, and Google Scholar. After removing duplicates from electronic databases

and excluding papers that were irrelevant to our objectives, 838 papers were eliminated, leaving 89 papers for screening based on titles, abstracts, and full texts. Subsequently, 68 articles were excluded because their results were either pertained to other plants (incorrect population), were written in languages other than English, or addressed topics unrelated to our focus on phytochemical constituents and pharmacological uses (incorrect outcomes). Finally, 21 studies were deemed eligible for inclusion in this review based on the established eligibility criteria.

3.2. Study characteristics

Table 1 summarizes the key characteristics of the final included studies, including study design, plant parts used, extraction methods, and conclusion.

4. SUMMARY OF FINDINGS

4.1. Phytochemical constituents of *Solanum dubium* (Syn: *Solanum coagulans*)

Phytochemicals, primarily secondary metabolites found in higher plants, play multiple and crucial roles in helping plants manage environmental stresses. Research has shown that these natural compounds (secondary metabolites) affect the physiology of humans, animals, fungi, and bacteria in both

direct and indirect ways (Sadeek and Abdallah, 2019). Several compounds were either isolated and identified or identified without isolation from *S. dubium*; Table 2 summarizes these natural compounds.

The seeds of *S. dubium* showed the presence of chymotrypsin-like serine protease and rennin-like enzymes, both were isolated, purified, and recognized as dubiumin and chymotrypsin serine-like protease enzyme, respectively. Dubiumin has a molecular mass of 66 kDa, while the second enzyme consists of three bands with molecular mass of 11 KD, 35 KD, and 40 KD; both enzymes demonstrated traditional uses of the seeds and berries in clotting milk of cow, goat, and sheep (Abbas and Abdelrahman, 2021; Mohamed Ahmed et al., 2009).

Zhang (2015) isolated 10 compounds from the whole plant of *S. coagulans* by using column chromatography and preparative high-performance liquid chromatography (prep. HPLC). Five compounds belonged to steroidal saponins (anguiviosides XV (1), smilaxchinoside A (2), methylprotodioscin (3), protodioscin (4), and solamargine (5). Other compounds flavanol glycosides (3',4',5-trihydroxy-7-methoxy-6-C- β -D-glucopyranoside (6), brainoside B (7), camsibriside A (8), kampferol-3-O-(2''- β -D-galactopyranosyl)- β -D-glucopyranoside (9), and quercetin-3-O-(2''- β -D-galactopyranosyl)- β -D-glucopyranoside (10) (Figure 4) (Zhang 2015).

Mohamed et al., 2016c studied the phytochemical constituents in the seeds of *S. dubium*; in their study, *S. dubium* seeds were crushed and macerated in 96% ethanol, followed

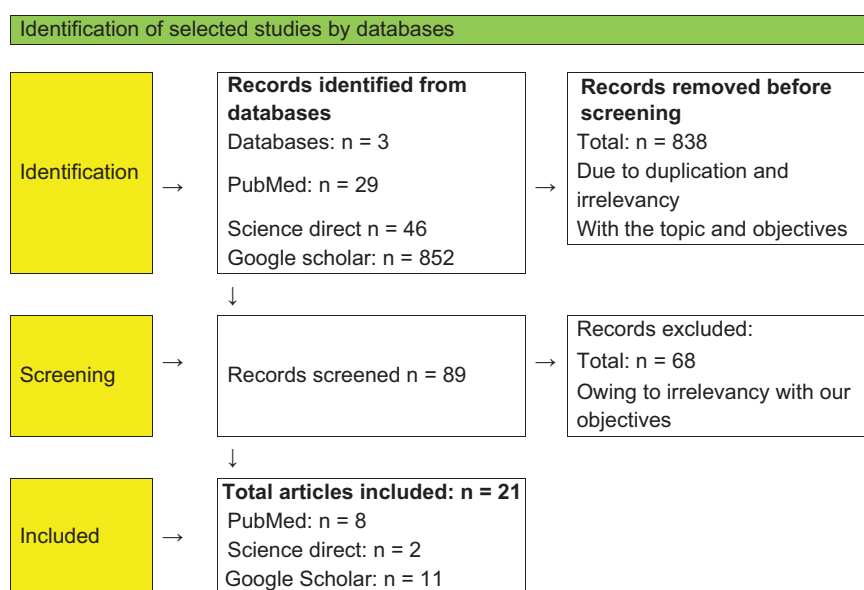


Figure 3. PRISMA flow chart.

Table 1

Summary of the key findings of the included studies.

No.	Study design	Part of the plant used	Extraction and preparation method	Conclusion	References
1.	Studying the toxicological profile by <i>in vivo</i> model of Wistar albino mice, different doses was administered orally	Seeds	Aqueous at an ambient temperature for 24 h	The results revealed absence of any mortality among all groups; also, there were no changes in both biochemical and hematological tests. The aqueous seeds extract of <i>S. dubium</i> was established to be safe with LD ₅₀ > 2000 mg/kg body weight (BW) of oral route of administration.	Mohamed et al., 2016a
2.	Isolation and purification via column chromatography and prep. HPLC <i>In vitro</i> cytotoxic activity against SMCC-7721 and NCI-H460 cell lines (human hepato-carcinoma and large-cell lung cancer, respectively)	Whole plant	Alcoholic/maceration	Ten compounds were isolated and identified; they were related to either steroidal saponins or flavonol glycosides. Two steroidal saponin compounds (protodioscin and solamargine) showed cytotoxic activity against SMCC-7721 and NCI-H460 cell lines.	Zhang, 2015
3.	Preliminary phytochemical screening	Roots	-	The roots showed presence of carbohydrates, saponins, alkaloids, tannin, and triterpenes; no phenolic compounds, flavonoids, and heavy metals (such as lead, arsenic, mercury, and cadmium) were detected.	Patel et al., 2018
4.	Isolation and purification of a chymotrypsin-like serine protease enzyme by using (NH ₄) ₂ SO ₄ fractionation, cation exchange, and gel filtration chromatographic methods	Seeds	5% NaCl in NaOAc buffer, pH 5.0, for 1 h with stirring at 4°C	A serine protease was purified 6.7-fold and with 35% recovery from the seeds. The enzyme, named dubiumin, has a molecular mass of 66 kDa.	Mohamed Ahmed et al., 2009
5.	<i>In vitro</i> antibacterial and antifungal activities by using cup plate agar diffusion method, either alone or combined with Sudanese Sunnut honey (1:4)	Seeds	Ethanol 96% and methanol 96% extracts (100 mg/mL each)/maceration.	Significant antibacterial and antifungal activities against <i>B. subtilis</i> , <i>S. aureus</i> , <i>E. coli</i> , <i>S. typhi</i> , <i>C. albicans</i> , and <i>A. niger</i> .	Mohamed et al., 2016b
6.	Isolation and identification by various chromatographic and spectroscopic methods <i>In vitro</i> antifungal activity	Aerial parts	Alcoholic extract/maceration	Methyl salicylate 2-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside and 12 other known phenolic compounds were isolated. Among them, neochlorogenicin 6-O-β-D-xylopyranosyl (1→3)-β-D-quinovopyranoside showed significant antifungal activity against <i>T. mentagrophytes</i> , <i>M. gypseum</i> , and <i>E. floccosum</i> with MIC values between 1.56 and 3.13 µg/mL.	Qin et al., 2016
7.	Isolation and purification of an enzyme by gel filtration and SDS-PAGE chromatographic methods	Seeds	Aqueous/cold method of extraction	Chymotrypsin, a serine-like protease enzyme was isolated, purified, and identified; it possesses milk clotting property.	Abbas and Abdelrahman, 2021
8.	Preliminary phytochemical screening <i>In vitro</i> , DPPH radical scavenging assay of <i>S. dubium</i> extracts, either alone or combined with honey	Seeds	96% ethanol/maceration The plant sample and honey were extracted by ethanol 96%, methanol, and distilled water	The seeds showed presence of alkaloids, flavonoids, sterols, triterpenes, coumarins, saponins, and tannins; no anthraquinones were detected. The aqueous extract combined with honey showed the highest antioxidant activity (about 91% RSA), while the aqueous extract of the plant alone and the aqueous extract of honey showed about 77% RSA and about 7% RSA, respectively. The ethanolic and methanolic extracts of <i>S. dubium</i> seeds showed about 83% and 80% RSA, respectively.	Mohamed et al., 2016c

(continues)

Table 1

Continued.

No.	Study design	Part of the plant used	Extraction and preparation method	Conclusion	References
9.	Preliminary phytochemical screening Isolation and partial identification by TLC, UV-Vis spectrophotometer, and NMR <i>In vitro</i> DPPH radical scavenging assay	Leaves	80% methanol/ maceration	The leaves showed presence of alkaloids, flavonoids, steroids, coumarins, saponins, and tannins. A chalcone molecule was isolated and partially identified. The methanolic extract showed significant antioxidant activity.	Athar et al., 2021
10.	Isolation, validation, and quantitative analysis of ellagic acid and gallic acid by HPTLC	Seeds	Methanol/ sonication at 40°C, then fractionated by ethyl acetate	The seeds extract was found to contain 1.1% w/w ellagic acid and 2.1% w/w gallic acid.	Mohamed et al., 2020
11.	Preliminary phytochemical screening Anti-schistosomiasis activity against <i>Biomphalaria pfeifferi</i> , an intermediate host of <i>Schistosoma mansoni</i>	Fruits	Ethanol 80%/ maceration	The fruits showed presence of alkaloids, flavonoids, sterols, coumarins, saponins, and tannins; no triterpenes and anthraquinones were detected. The fruits extract was tested for several doses; it exhibited molluscicidal property with $LC_{50} = 153.02$ ppm and $LC_{90} = 226.62$ ppm.	Albagouri et al., 2021
12.	Evaluation of minerals content	Seeds	Aqueous/shacking till homogenous	The seeds showed presence of various amounts of some heavy metals and basic metals, such as Mn, Cr, Cd, Zn, Fe, Ca, Mg, K, and P.	Mohammed, 2017
13.	Studying the toxicity of oral administration of dried and minced fruits of <i>S. dubium</i> on Nubian goats, Desert sheep, and Zebu calves	Fruits	-	Significant reduction in synthesis of proteins by the livers and renal dysfunctions. At doses of 2.5–10 gm/kg/day, the minced fruits killed all goats in 2–5 days, while all sheep took longer period to get killed.	Barri et al., 1983
14.	<i>In vitro</i> anticancer and antimicrobial activities on human liver (HepG2) and kidney (HEK-239) cell lines <i>In vitro</i> antimicrobial activity against <i>S. aureus</i> , <i>E. coli</i> , <i>P. aeruginosa</i> , and <i>C. albicans</i>	Aerial parts	Ethanol extract	The extract showed significant cytotoxic effects on liver and renal cells, with $IC_{50} = 28.4$ µg/mL and 25.7 µg/mL, respectively. The same extract exhibited remarkable antimicrobial activity, the MIC ranged between 0.4 mg/mL and 3.2 mg/mL, the zone of inhibitions ranged between 17 mm and 22 mm.	Alajmi et al., 2018
15.	<i>In vitro</i> anti-acne activity against <i>Propionibacterium acnes</i> <i>In vitro</i> DPPH radical scavenging assay	Fruits	Methanol 50% and ethanol 50%/ maceration	The ethanolic extract showed anti-acne activity with MIC = 4 mg/mL, the methanolic extract was inactive. DPPH radical scavenging activity (RSA) revealed that IC_{50} values of methanolic and ethanolic extracts were about 10.66 and 13.77 µg/mL, respectively.	Muddathir and Mitsunaga, 2013
16.	<i>In vitro</i> antibacterial and antifungal activities by using agar disc diffusion method and potato dextrose media, respectively <i>In vitro</i> antioxidant, total phenolics and flavonoids content	Seeds	Methanol 80%/ Soxhlet's apparatus at 60°C	Methanolic extract (50 µg/mL) showed significant antibacterial and antifungal activities. The results revealed zone of inhibitions of 9.8, 8.9, 9.8, 10.4, 8.8, and 9.1 mm of <i>E. ludwigii</i> , <i>Pseudomonas</i> sp., <i>O. oryzae</i> , <i>S. maltophilia</i> , <i>P. aeruginosa</i> , and <i>E. coli</i> , respectively. The fungal organism used was <i>Curvularia</i> sp., the results showed zones of inhibition of 26, 23, and 10 mm at 6, 12, and 25 mg/mL, respectively. The results showed 95.78% of free radical scavenging activity, high phenolic and flavonoids content.	Radwan et al., 2019

(continues)

Table 1

Continued.

No.	Study design	Part of the plant used	Extraction and preparation method	Conclusion	References
17.	<i>In vitro</i> antioxidant activity by using DPPH and ABTS assays Quantitative analysis of total phenolics, flavonoids and carotenoids content	Fruits	Successive extraction by n-hexane, ethyl acetate, and ethanol/refluxing	The study concluded that there is a strong co-relation between the antioxidant activity and the total phenolics and flavonoids content of each extract.	Fidrianny et al., 2015
18.	<i>In vitro</i> antioxidant activity by using FRAP, CUPRAC, H ₂ O ₂ -scavenging, phospho-molybdenum, and BCB methods Quantitative analysis of total phenolics content (TPC), total flavonoids content (TFC), and total carotenoids content (TCC)	Fruits	Successive extraction by n-hexane, ethyl acetate, and ethanol/refluxing	The TPC of all extracts had a tendency to correlate with FRAP and H ₂ O ₂ scavenging antioxidant capacity, while TFC and TCC had a tendency to correlate with CUPRAC, phospho-molybdenum, and BCB antioxidant capacity. The study concluded that phenolic compounds were a major contributor in antioxidant capacity by using FRAP and H ₂ O ₂ scavenging assays, while flavonoids and carotenoids were the major contributors of antioxidant capacity by using CUPRAC, phosphomolybdenum, and BCB assays.	Fidrianny et al., 2016
19.	<i>In vivo</i> antidiabetic activity using Wister albino mice	-	Ethanol extract	The results revealed the presence of significant hypoglycemic activity that rapidly lowers blood glucose, especially in 200 mg/kg group (25.35% reduction of blood glucose level), but their effects were short-lived (short acting, compared to glibenclamide group). The alcoholic extract also showed strong synergistic effect with insulin via enhancing glucose uptake inside the tissues by using rat's hemi-diaphragm model.	Sulaiman et al., 2016
20.	<i>In vivo</i> anti-hyperlipidemic activity on Wistar albino mice	Fruits	Ethanol extract	The results showed significant improvements in lipid profiles, particularly in reducing low-density lipoprotein (LDL) levels, along with notable weight changes.	Sulaiman et al., 2015
21.	<i>In vitro</i> inhibitory activity on HIV-1 viral replication	Fruits	Methanol and aqueous extracts/refluxing	Both extracts were inactive on HIV-induced cytopathic effects (CPE) on MT-4 cells, with an HIV-1 percentage inhibition of about 7.9% and 4.6% for methanolic and aqueous extracts, respectively.	Hussein et al., 1999

Notes: LD₅₀: lethal dose 50%; MIC: minimum inhibitory concentration; HPTLC: high-performance thin layer chromatography; HIV: human immunodeficiency virus; SDS-PAGE: sodium dodecyl sulfate–polyacrylamide gel electrophoresis.

by filtration. The filtrates were then pooled, and the solvent was evaporated by using rotary evaporator; the seeds showed the presence of alkaloids, flavonoids, sterols, triterpenes, coumarins, saponins, and tannins; no anthraquinones were detected (Table 3) (Mohamed et al., 2016c).

Athar et al. (2021) studied the phytochemical constituents in *S. dubium* leaves. A sample of powdered *S. dubium* leaves was macerated in 80% aqueous methanol for 3 days. The leaves showed the presence of alkaloids, flavonoids, steroids, coumarins, saponins, and tannins (Table 3) (Athar et al., 2021).

Albagouri et al. (2021) studied the phytochemical contents of *S. dubium* fruits (Table 3). Briefly, 50 g of the plant material

powder was soaked in 500 mL of 80% aqueous ethanol in Erlenmeyer flasks and left for 72 h with periodic stirring. The mixture was filtered, and the filtrate was concentrated under reduced pressure. The concentrated extract was placed in a pre-weighed petri dish and left to dry thoroughly at room temperature. The remaining residue was reintroduced into the flask with the recovered solvent for additional extraction. This process was repeated for three times to ensure that the plant material was fully extracted. The final dried extract was tested for preliminary phytochemical screening. The fruits showed the presence of alkaloids, flavonoids, sterols, coumarins, saponins, and tannins; no triterpenes and anthraquinones were detected (Albagouri et al., 2021).

Table 2Summary of names of phytochemicals isolated and/or identified from *S. dubium*.

No.	Compound name	Chemical class	Part of plant	Known activities	References
1.	Anguiviosides XV	Steroidal saponin	Whole plant	Anti-inflammatory, antioxidant, anticancer	Zhang, 2015
2.	Smilaxchinoside A	Steroidal saponin	Whole plant	Anti-inflammatory, antioxidant, anticancer, cardiovascular benefits	Wang et al., 2024; Zhang, 2015
3.	Methylprotodioscin	Steroidal saponin	Whole plant	Anti-inflammatory, antioxidant, anticancer, cardiovascular benefits, immunomodulatory effects, hypoglycemic, antiviral, hepatoprotective, hypolipidemic	Chen et al., 2023; Zhang, 2015
4.	Protodioscin	Steroidal saponin	Whole plant	Anti-inflammatory, antioxidant, anticancer, cardiovascular benefits, immunomodulatory effects, hypolipidemic, sexual effects	Chen et al., 2022; Zhang, 2015
5.	Solamargine	Steroidal glycol-alkaloid	Whole plant	Anti-inflammatory, antioxidant, anticancer, antimicrobial, hepatoprotective, neuroprotective, molluscicidal, schistosomicidal, antiprotozoal, antiparasitic	Delbrouck et al., 2023; Zhang, 2015
6.	3',4',5-trihydroxy-7-methoxy-6-C-β-D-glucopyranoside	Flavanol glycoside	Whole plant	Anti-inflammatory, antioxidant, antimicrobial	Zhang, 2015
7.	Brainoside B	Flavanol glycoside	Whole plant	Anti-inflammatory, antioxidant, neuroprotective, cognitive enhancement, antidepressant	
8.	Camsibriside A	Flavanol glycoside	Whole plant	-	
9.	Kampferol-3-O-(2"-β-D-galactopyranosyl)-β-D-glucopyranoside	Flavanol glycoside	Whole plant	Multiple pharmacological uses	
10.	Quercetin-3-O-(2"-β-D-galactopyranosyl)-β-D-glucopyranoside	Flavanol glycoside	Whole plant	Multiple pharmacological uses	
11.	Methyl salicylate 2-O-β-D-glucopyranosyl-(1→2)-β-D-glucopyranoside	Phenolic compound	Aerial parts	Methyl salicylate has multiple pharmacological uses	Michel and Olszewska, 2024; Qin et al., 2016
12.	Gallic acid	Phenolic compound	Seeds	Anti-inflammatory, antioxidant, antitumor, antibacterial, antimicrobial, antidiabetic, antiobesity, anti-myocardial ischemia	Bai et al., 2021; Mohamed et al., 2020
13.	Ellagic acid	Phenolic compound	Seeds	Anti-inflammatory, antioxidant, neuroprotective, anti-Alzheimer, antidiabetic, anti-hyperlipidemic, antibacterial, antifungal, antiviral, antiparasitic, adjunctive in treatment of cancer, hepatoprotective	Golmei et al., 2024; Mohamed et al., 2020
14.	Rutin	Flavanol/flavonoid	Aerial parts	Cytotoxic, antibacterial, anti-genotoxic, anti-inflammatory, antioxidant, cardiovascular benefits, neuroprotective, antidiabetic	Akinboro et al., 2020; Alajmi et al., 2018

Table 3Summary of phytoconstituents present in seeds, leaves, fruits, and roots of *Solanum dubium*.

Secondary metabolites	<i>Solanum dubium</i> seeds (Mohamed et al., 2016c)	<i>Solanum dubium</i> leaves (Athar et al., 2021)	<i>Solanum dubium</i> fruits (Albagouri et al., 2021)	<i>Solanum dubium</i> roots (Patel et al., 2018)
Alkaloids	+	+	+	+
Flavonoids	+	+	+	-
Tannins	+	+	+	+
Saponins	+	+	+	+
Coumarins	+	+	+	NIL
Anthraquinones	-	-	-	-
Sterols	+	+	+	NIL

Notes: "+" present, "-" absent, and "NIL" not in laboratory.

Patel et al. (2018) studied the content of phytochemical constituents in *S. dubium* roots (Table 3). The freshly collected plant samples were powdered and examined; the roots showed the presence of carbohydrates, saponins, alkaloids, tannin, and triterpenes; no phenolic compound, flavonoid, and heavy metals (such as lead [Pb], arsenic [As], mercury [Hg], and cadmium [Cd]) were detected (Patel et al., 2018).

Arthar et al. (2021) isolated and partially identified a chalcone molecule (11) (Figure 4) from the methanolic extract of *S. dubium* leaves. Thin layer chromatography (TLC) was applied for its isolation, while ultraviolet (UV) and nuclear magnetic resonance (NMR) were applied for its partial identification; the methanolic extract showed significant antioxidant activity by using 2,2-diphenyl-1-picrylhydrazyl (DPPH)-radical scavenging assay (Arthar et al., 2021).

Qin et al. (2016) isolated and identified methyl salicylate 2-O- β -D-glucopyranosyl-(1 $\rightarrow$ 2)- β -D-glucopyranoside (12) (Figure 4) besides 12 phenolic compounds from the aerial parts of *S. coagulans*. They were identified as isorhamnetin 3-O- β -D-glucopyranoside (13), N-p-coumaroyltyramine (14), neochlorogenin 6-O- β -D-xylopyranosyl (1 $\rightarrow$ 3)- β -D-quinovopyranoside (15), quercetin 3-O- β -D-galactopyranoside (16), syringaresinol (17), neochlorogenin 6-O- α -L-rhamnopyranosyl(1 $\rightarrow$ 3)- β -D-quinovopyranoside (18), radulignan (19), 22R, 23S, 25R)-3 β , 6 α , 23-trihydroxy-5 α -spirostane 6-O- β -D-xylopyranosyl (1 $\rightarrow$ 3)- β -D-quinovopyranoside (20), torvoside M (21), torvoside K (22), torvoside L (23), and (22R, 23R, 25S)-3 β , 6 α , 23-trihydroxy-5 α -spirostane 6-O- β -D-xylopyranosyl (1 $\rightarrow$ 3)-O- β -D-quinovopyranoside (24). Among the tested compounds, compound (15) revealed significant antifungal activity against *Trichophyton mentagrophytes*, *Microsporum gypseum*, and *Epidermophyton floccosum* with minimum inhibitory concentration (MIC) between 1.56 μ g/mL and 3.13 μ g/mL (Qin et al., 2016).

Mohamed et al. (2020) isolated and quantified gallic acid (25) and ellagic acid (26) (Figure 4) from *S. dubium* seeds by using high-performance thin layer chromatography (HPTLC). The seeds extract was found to contain 1.1% w/w ellagic acid and 2.1% w/w gallic acid.

The minerals content of *S. dubium* seeds was evaluated; it showed the presence of some heavy as well as basic metals, such as manganese (Mn), chromium (Cr), Cd, zinc (Zn), ferric (Fe), calcium (Ca), magnesium (Mg), potassium (K), and phosphorus (P) (Mohammed 2017).

4.2. Pharmacological activities of *Solanum dubium*

4.2.1. Toxicological studies

The aqueous extract of *S. dubium* seeds is used traditionally in alleviating asthma attacks. Hence, the acute toxicological

profile of the aqueous extract of the plant's seeds was conducted with Wistar albino mice; the animals were randomly divided into several groups and afforded experimental doses of 2 mL/kg/day, 10 mL/kg/day, 20 mL/kg/day, and 40 mL/kg/day of the aqueous extract and examined in each group for 7 continuous days. Biochemical assay, hematological test, liver function test, and renal function test were conducted to confirm any toxicity related to the aqueous extract. The results revealed absence of any mortality among all groups; also, there were no changes in both biochemical and hematological tests. The aqueous extract of *S. dubium* seeds was established to be safe with LD₅₀ > 2000 mg/kg body weight (BW) through oral route of administration. This observation emphasizes the safety of aqueous extract of *S. dubium* seeds across a wide range of doses (Mohamed et al., 2016a).

On the other hand, Barri et al. (1983) studied the toxicity of oral administration of the dried and minced fruits of *S. dubium* on the Nubian goats, Desert sheep, and Zebu calves. Clinical and hematological investigations showed significant reduction in the synthesis of proteins through liver and renal dysfunctions. At doses of 2.5–10 gm/kg/day, the minced fruits terminated all goats in 2–5 days, while all sheep took longer period to succumb (Barri et al., 1983).

4.2.2. Cytotoxic activity

Two steroidal saponins were first isolated and characterized from the whole plant of *S. coagulans*. Both compounds (i.e., protodioscin (4) and solamargine (5)) were tested *in vitro* for cytotoxic properties by using SMCC-7721 and NCI-H460 cell lines of human hepato-carcinoma and large-cell lung cancer, respectively. Both compounds showed significant cytotoxic activity by using both cell lines, demonstrating the importance of steroidal saponins in developing new molecules with anticancer activity (Zhang 2015).

The ethanolic aerial parts of *S. coagulans* were prepared and tested for anticancer activity. Human liver (HepG2) and kidney (HEK-239) cell lines were applied *in vitro*. The extract showed significant cytotoxic effects on liver and renal cells, with IC₅₀ = 28.4 μ g/mL and 25.7 μ g/mL, respectively. Fluorouracil was used as positive control (Alajmi et al., 2018).

4.2.3. Antimicrobial activity

Both ethanolic and methanolic extracts of *S. dubium* seeds, either alone or combined with Sudanese Sunnut honey (1:4), had shown significant antimicrobial activity against four standard bacterial strains and two standard fungal strains by using the cup plate agar diffusion method. The bacterial organisms were *B. subtilis*, *S. aureus*, *E. coli*, and *Salmonella typhi*. The tested fungal organisms were *Candida albicans* and *Aspergillus niger*. The concentration of both ethanolic and methanolic extracts and their combinations with honey (1:4) was

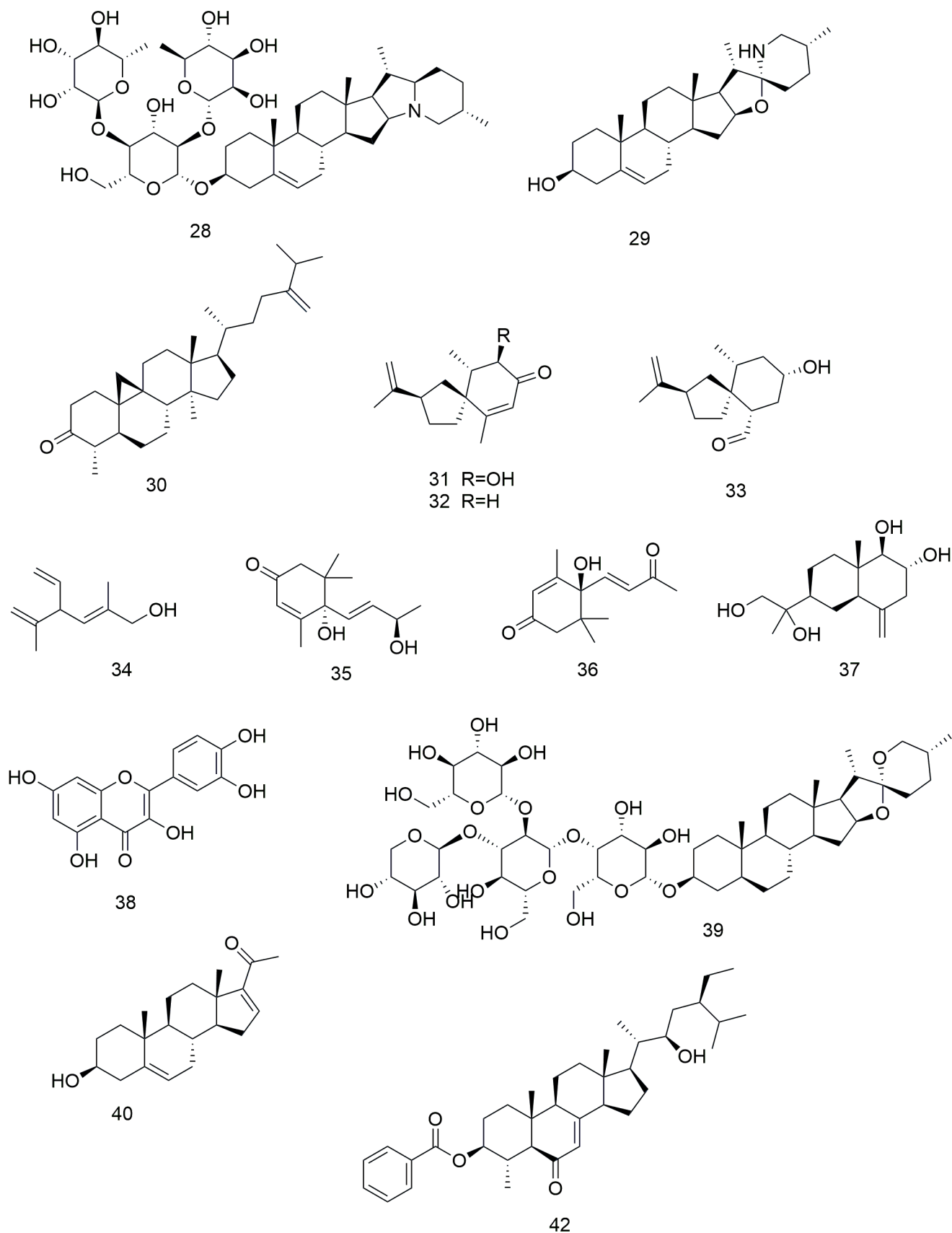


Figure 4. Structure of compounds isolated from *S. coagulans*.

100 mg/mL. The results revealed significant antibacterial activity of the ethanolic extract and its combination with honey on all bacterial species, the zone of inhibition ranged from 25.0 to 27.3 mm and 20.7 to 28.5 mm, respectively. The results also showed moderate antifungal activity of the ethanolic extract and its combination with honey, with range of zone of inhibition being 18.0 mm and 14.0–15.7 mm, respectively. On the other hand, the methanolic extract and its combination with honey showed significant antibacterial activity on all bacterial species. The zone of inhibition ranged from 25.0 to 27.0 mm and 20.0 to 28.5 mm, respectively; while both samples revealed moderate antifungal activity against all tested fungal species with range of zone of inhibition being 16.0–18.0 mm and 15.0–16.0 mm, respectively. Ampicillin, gentamycin, clotrimazole, and nystatin were used as standard positive controls. This suggests that *S. dubium* seeds could be valuable for antimicrobial activity, either alone or combined with honey. The study also suggested the activity, probably because of the abundance of steroidal alkaloids, tannins, and flavonoids in Solanaceous plants as general (Mohamed et al., 2016b).

The ethanolic aerial part of *S. coagulans* was prepared and tested for antimicrobial activity. The alcoholic extract exhibited remarkable antimicrobial activity against *Staphylococcus aureus*, *E. coli*, *P. aeruginosa*, and *Candida albicans*; the MIC ranged from 0.4 to 3.2 mg/mL, and the zone of inhibition was between 17 mm and 22 mm. The study suggested the presence of high content of rutin (27) (Figure 4), attributed to both cytotoxic and antimicrobial activities (Alajmi et al., 2018).

On the other hand, both methanolic and ethanolic 50% extracts of *S. dubium* fruits were obtained by maceration and examined *in vitro* against *Propionibacterium acnes* (*Cutibacterium acnes*), the causative bacteria of acne. The ethanolic extract showed anti-acne activity with MIC = 4 mg/mL; the methanolic extract was inactive. The DPPH radical scavenging activity (RSA) revealed that IC₅₀ of methanolic and ethanolic extracts were about 10.66 µg/mL and 13.77 µg/mL, respectively. This was regarded as mild to weak anti-acne activity of alcoholic extracts of *S. dubium* fruits (Muddathir and Mitsunaga, 2013).

In addition, the hydro-methanolic extract (80%) of *S. coagulans* seeds was extracted at 60°C by Soxhlet's apparatus and investigated for antibacterial and antifungal activities. The methanolic extract (50 µg/mL) showed significant antibacterial and antifungal activity by using agar disc diffusion method and potato dextrose media, respectively; the tested bacterial organisms were *Enterobacter ludwigii*, *Pseudomonas* sp., *Ochrobactrum oryzae*, *Bacillus subtilis*, *Stenotrophomonas maltophilia*, *Pseudomonas aeruginosa*, *E. coli*, *Micrococcus luteus*, *Nesterenkonia halobia*, and *Streptomyces parvulus*; the

results revealed zone of inhibition as follows: *E. ludwigii* (9.8 mm), *Pseudomonas* sp. (8.9 mm), *O. oryzae* (9.8 mm), *S. maltophilia* (10.4 mm), *P. aeruginosa* (8.8 mm), and *E. coli* (9.1 mm); streptomycin was applied as a positive control. The fungal microorganism used was *Curvularia* sp., the results showed zone of inhibition being 26, 23, and 10 mm at 6, 12, and 25 mg/mL, respectively (Radwan et al., 2019).

4.2.4. Antioxidant activity

The antioxidant activity of *S. dubium* seeds was examined by using the DPPH-free radical scavenging activity assay. Propyl gallate was used as a positive control. The plant sample and honey were extracted by 96% ethanol, methanol, and distilled water. The aqueous extract of the plant combined with honey showed the highest antioxidant activity (about 91% RSA), while the aqueous extract of the plant and its aqueous extract with honey showed about 77% RSA and about 7% RSA, respectively. Propyl gallate (the positive control) showed about 93% RSA. Both ethanolic and methanolic extracts of *S. dubium* seeds showed about 83% RSA and about 80% RSA, respectively. Phytochemical screening of three extracts of *S. dubium* seeds revealed the presence of alkaloids, tannins, sterols, triterpenes, flavonoids, coumarins, and saponins. The study recommended that the antioxidant activity of these extracts could serve as natural and food supplement antioxidants, potentially aiding in the treatment of free radical-related diseases, such as cancer, diabetes, and inflammation. Additionally, the study suggested applying bio-guided isolation and characterization of active natural compounds (Mohamed et al., 2016c).

Likewise, the hydro-methanolic extract (80%) of *S. coagulans* seeds was extracted at 60°C by Soxhlet's apparatus and investigated for antioxidant activity, and TPC and TFC. Polyphenolic content was estimated by using gallic acid as control, the concentration was measured at 765 nm and calculated as µg gallic acid dry weight equivalent (GAE/gm DW). The results showed high phenolic content of 206.65 mg GAE/gm dry tissue. The flavonoids content was evaluated as µg catechin dry weight equivalent (CE/gm DW). The flavonoid concentration was read at 510 nm, and the extract showed high flavonoid content (12.66 mg CE/gm DW). The antioxidant activity was investigated by the DPPH free radical scavenging method; the absorbance of both sample and blank was read at 517 nm, the percentage free RSA being 95.78%; vitamin C was applied as a positive control (Radwan et al., 2019).

The antioxidant activity of *S. coagulans* fruits was studied by using *in vitro* DPPH and ABTS assays. The fruits were successively extracted by n-hexane, ethyl acetate, and ethanol via refluxing method; the collected extracts were also treated for quantitative analysis to estimate TPC, TFC, and TCC.

The IC_{50} value of DPPH RSA of the ethanolic extract was 3 $\mu\text{g}/\text{mL}$, compared to vitamin C (standard), which was 0.1 $\mu\text{g}/\text{mL}$. The IC_{50} of ABTS scavenging activity was 1.5 $\mu\text{g}/\text{mL}$. The absorbance of IC_{50} of DPPH and ABTS scavenging activities were measured at wavelengths of 516 nm and 734 nm, respectively. The ethyl acetate extract showed weak antioxidant activity with both assays. The TPC of the ethanolic extract was estimated and expressed as quercetin equivalent (0.44 g QE/100 g) and gallic acid equivalent (4.34 g GAE/100 g); the TPC of ethyl acetate extract was 2.62 g GAE/100 g. The TFC of n-hexane extract was 2.57 g QE/100 g. The TCC of the ethanolic extract was 0.01 g β -carotene equivalent (BE)/100 g. The study concluded that there was a strong correlation between the antioxidant activity and TPC and TFC of each extract (Fidrianny et al., 2015).

Another study investigated the antioxidant capacity of *S. coagulans* fruits using five different assays: ferric reducing antioxidant power (FRAP), cupric reducing antioxidant capacity (CUPRAC), H_2O_2 -scavenging, phosphomolybdenum assay, and β -carotene bleaching (BCB) methods. The IC_{50} and EC_{50} values for all five methods were estimated and correlated with TPC, TFC, and TCC of plant extracts. The plant samples were successively extracted using n-hexane, ethyl acetate, and ethanol through reflux extraction. The antioxidant capacity was measured using a UV-VIS spectrophotometer, and the correlation with IC_{50} values of five methods was analyzed using Pearson's method. The EC_{50} values for FRAP of n-hexane, ethyl acetate, and ethanolic extracts were approximately 400 $\mu\text{g}/\text{mL}$, 90 $\mu\text{g}/\text{mL}$, and 115 $\mu\text{g}/\text{mL}$, respectively. The same sequence of extracts yielded EC_{50} values for CUPRAC of about 220 $\mu\text{g}/\text{mL}$, 170 $\mu\text{g}/\text{mL}$, and 580 $\mu\text{g}/\text{mL}$, respectively. The IC_{50} values for H_2O_2 -scavenging were approximately 14 $\mu\text{g}/\text{mL}$, 13.5 $\mu\text{g}/\text{mL}$, and 1 $\mu\text{g}/\text{mL}$, respectively, while the EC_{50} values for the phosphomolybdenum capacity of the same extracts were around 1800 $\mu\text{g}/\text{mL}$, 300 $\mu\text{g}/\text{mL}$, and 4,800 $\mu\text{g}/\text{mL}$, respectively. Lastly, the EC_{50} values for the BCB assay were approximately 1400 $\mu\text{g}/\text{mL}$, 158 $\mu\text{g}/\text{mL}$, and 1,700 $\mu\text{g}/\text{mL}$, respectively. Among the extracts, ethyl acetate exhibited the highest antioxidant capacity, followed by the ethanolic extract, while n-hexane extract demonstrated weak antioxidant capacity. The TPC of the extracts in the same sequence was about 0.6 g GAE/100 g, 2.62 g GAE/100 g, and 4.34 g GAE/100 g, respectively. The TFC was approximately 2.57 g QE/100 g, 5.45 g QE/100 g, and 0.44 g QE/100 g, respectively, and the TCC was approximately 0.087 g BE/100 g, 0.12 g BE/100 g, and 0.0088 g BE/100 g, respectively. The TPC of all extracts showed a tendency to correlate with the FRAP and H_2O_2 -scavenging antioxidant capacities, while TFC and TCC tended to correlate with CUPRAC, phosphomolybdenum, and BCB antioxidant activity. Therefore, the

study concluded that phenolic compounds were the major contributors to antioxidant activity as measured by FRAP and H_2O_2 -scavenging assays, while flavonoids and carotenoids were the primary contributors as assessed by CUPRAC, phosphomolybdenum, and BCB assays (Fidrianny et al., 2016).

4.2.5. Anti-schistosomiasis activity

The hydro-ethanolic extract of *S. dubium* fruits was established to have remarkable activity against snails (*Biomphalaria pfeifferi*), an intermediate host of *Schistosoma mansoni*, which is mainly responsible of endemic intestinal schistosomiasis in many regions. *S. dubium* fruits extract was tested at different doses (1000, 500, 250, 100, 50, and 25 ppm) against snails and exhibited molluscicidal property with $LC_{50} = 153.02$ ppm and $LC_{90} = 226.62$ ppm, indicating feasible utilization for eradication of intestinal schistosomiasis. The researchers suggested isolation and identification of active natural compounds (Albagouri et al., 2021).

4.2.6. Antidiabetic activity

The alcoholic extract of *S. dubium* was examined for antidiabetic activity. Wistar albino mice were divided into different groups: three groups were treated with various concentrations of alcoholic extract (i.e., 100, 200, and 400 mg/kg BW), while other groups were treated with glibenclamide (10 mg/kg BW) and distilled water (10 mL/kg BW) as positive and negative groups, respectively. The results revealed presence of significant hypoglycemic activity that rapidly decreased blood glucose levels, especially in the 200 mg/kg group (25.35% reduction in blood glucose level), but their effects were short-lived (short acting, compared to the glibenclamide group). The alcoholic extract also showed strong synergistic effect with insulin by enhancing glucose uptake inside the tissues by using rat's hemidiaphragm model. The study concluded by suggesting the presence of potential compounds, which are to be isolated and elucidated for further investigations (Sulaiman et al., 2016).

4.2.7. Anti-hyperlipidemic activity

The anti-hyperlipidemic activity of the ethanolic extract of *S. dubium* fruits was examined on Wistar albino mice by using a standard model. The animals were randomly scattered in different groups; atorvastatin (10 mg/kg BW) was used as a positive control, while the ethanolic extract of *S. dubium* fruits was administered at a dose of 400 mg/kg/day BW. The total lipid profile levels (i.e., cholesterol, triglycerides, low-density lipoprotein [LDL], and high-density lipoprotein [HDL]) were analyzed with animal blood samples (at days: 0, 14, and 30). In addition, the body weight of mice was checked regularly during the assay. The study found that mice treated with

S. dubium fruits extract showed significant improvement in their lipid profiles, particularly in reducing LDL levels, along with notable changes in weight. These results suggested the potential of *S. dubium* in managing hyperlipidemia. The researchers recommended in their study to conduct isolation and structured elucidation process to determine responsible active molecules (Sulaiman et al., 2015).

4.2.8. Anti-HIV activity

The methanolic and aqueous extracts of *S. dubium* fruits were prepared by refluxing for 3 h. Both extracts were screened for their inhibitory activity on HIV-1 viral replication. Both extracts were inactive on HIV-induced cytopathic effects (CPE) on MT-4 cells (*in vitro*), with HIV-1 percentage inhibition of about 7.9% and 4.6% for methanolic and aqueous extracts, respectively; the applied concentration was 100 µg/mL (Hussein et al., 1999).

5. DISCUSSION

Solanum dubium (Solanaceae) is a plant that has garnered considerable attention because of its diverse non-pharmacological, traditional, and pharmacological applications. It is known to possess a wide range of medicinal and non-medicinal properties, which are documented in both traditional and modern literature. In this review, we aimed to highlight the published research articles on the plant's phytochemical constituents and pharmacological activities.

The Solanaceae family is known for providing important active compounds with significant applications in pharmacy. For example, tropane alkaloids, such as atropine and hyoscyne, are abundant in this family and are concentrated in the species such as *Datura stramonium*, *Atropa belladonna*, and *Hyoscyamus niger*. These compounds have various pharmacological uses because of their muscarinic antagonistic properties (Al-Ashaal et al., 2013; Shah et al., 2013). Additionally, anabasine and nicotine are pyridine alkaloids found in *Nicotiana tabacum*, and are used as insecticidal agents (Chowański et al., 2016).

Solanum is a genus and an important member of the Solanaceae family. Many plants belonging to this genus provide significant active phytochemicals with versatile pharmacological activities (Figure 5). For example, chaconine (28) is a glycoalkaloid found in *S. tuberosum* and used as a fungicidal agent. Solasodine (29) is a steroidal alkaloid isolated from the unripe fruits of *S. nigrum*, exhibiting antimicrobial, anti-inflammatory, and anticancer activities (Patel et al., 2013; Saleem et al., 2009). Triterpenes and sesquiterpenes are also abundant in *Solanum* species, primarily characterized by their anticancer and antifungal properties. For

instance, cycloeucalenone (30) is a triterpene derived from the leaves of *S. cernuum*, demonstrating significant anticancer and anti-nociceptive properties linked to COX-2 inhibition. Similarly, sesquiterpenes, such as 3-β-hydroxysolavetivone (31), solavetivone (32), and lubimin (33) from the roots of *S. abutiloides* exhibit antifungal activity against *Fusarium oxysporum*. Compounds such as lyratol D (34), blumenol A (35), dehydrovomifoliol (36), and lyratol C (37) are sesquiterpenes from *S. lyratum* with strong cytotoxic effects (Saleem et al., 2009). Quercetin (38) is a flavanol, which has potent antioxidant property and is also widely distributed in *Solanum* species, such as *S. nigrum* and *S. villosum* (Ud-Din et al., 2009; Zahara et al., 2019). Saponins are also found in *Solanum* species, and many saponins in the Solanaceae family have demonstrated antitumor, antiviral, anti-mycotic, and hypolipidemic activities. For instance, degalactotigonin (39), a known saponin isolated from *S. nigrum*, has shown anticancer properties (Chen et al., 2021; Zhao et al., 2018). Pregnane glycosides, from certain *Solanum* species, have demonstrated anticancer properties. For instance, 16-dehydropregnenolone (40), from the whole plant of *S. lyratum*, has shown significant cytotoxic activity against several cell lines; also, 5α-pregn-16-en-3,20-dione-6α-ol-6-O-[α-l-rhamnosyl-(1-3)-β-D-quinovoside] (41), from the fruits of *S. torvum*, has exhibited significant cytotoxic effect (Winkiel et al., 2022). A number of sterols have been isolated from *S. capsicoides*. Carpesterol (42), obtained from the seeds of *S. capsicoides*, is of medicinal significance because of its anti-proliferative activity against various cancer cell lines, and having antifungal properties (Kaunda and Zhang 2019).

Kaunda and Zhang (2019) reviewed phytochemical constituents and their pharmacological properties derived from 66 species of *Solanum* (*S. dubium* was not included). Their study identified more than 670 phytochemical constituents belonging to various groups, such as steroidal saponins, steroidal alkaloids, terpenes, flavonoids, lignans, sterols, phenolic compounds, coumarins etc. These phytochemical groups were established from different parts of *S. dubium* (Table 3). The following pharmacological activities were reviewed by Kaunda and Zhang (2019): analgesic, anthelmintic, anti-allergic, antianemic, antiasthmatic, antibacterial, anticancer, anticonvulsant, antidepressant, antidiabetic, antifungal, antihistaminic, antihypertensive, anti-inflammatory, anti-leishmanial, anti-melanogenetic, anti-molluscicidal, anti-nociceptive, anti-psoriatic, anti-plasmodial, antiprotazoal, anti-trypanosomal, anti-urolithiatic, antiviral, cardiovascular, diuretic, hepatoprotective, hypolipidemic, mosquito-larvicidal, nephrotoxic, spasmolytic, schistosomicidal, and vasorelaxant. Table 4 summarizes phytochemical groups and parts of the plant of the *Solanum* species from which phytochemical compounds were isolated, linked with their pharmacological properties.

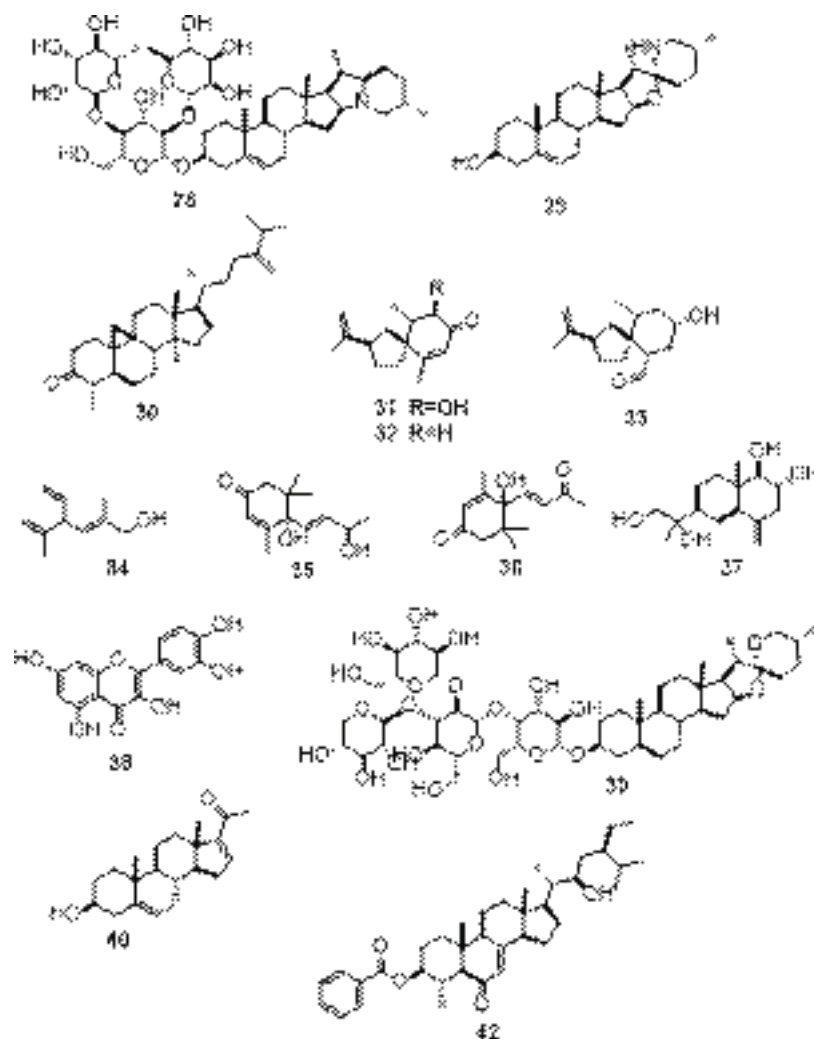


Figure 5. Chemical structures of some active constituents isolated from *Solanum* species, having significant pharmacological uses.

By comparing the previous information of our plant (*S. dubium*), we observed that it contained alkaloids, tannins, flavonoids, phenolic compounds, coumarins, sterols, and saponins; these phytochemical groups are distributed throughout the various parts of *S. dubium* (Table 3); however, in the field of bio-assay-guided fractionation, isolation, purification, identification, and structure elucidation of active natural compounds present in *S. dubium*, little research is conducted (Table 5); even the total number of available articles was small (only 21 articles), compared to other *Solanum* species (Figure 6). It was observed that most research were conducted on the seeds and fruits, while very few studies were done on the aerial parts, whole plant, roots, and leaves. We also found that isolated, characterized, and identified compounds were phenolic compounds, steroidal saponins, and flavonoids only (Table 2). There were no isolated and identified phytochemical compounds related to alkaloids, sterols,

and coumarins, although these groups demonstrated remarkable pharmacological uses (Table 4). Therefore, this gap should be considered and filled by researchers to attempt bio-assay-guided fractionation and identification of active compounds in *S. dubium*.

We also observed very few published research articles on the pharmacological activities of *S. dubium* (Table 6). Most articles focused on antimicrobial and antioxidant activities. In addition, the seeds and fruits dominated, while very few articles had examined the pharmacological activities of the whole plant, aerial parts, and leaves. The roots were never examined for any pharmacological activity, despite their richness of important secondary metabolites (Table 3). On the other hand, the plant showed significant antioxidant activity, which suggests that the plant could serve as a natural antioxidant aiding in the treatment of many oxidative stress-related diseases, such as cancer, inflammation, diabetes, cardiovascular

Table 4

Summary of phytochemical compounds isolated from *Solanum* species, including their phytochemical groups, plant parts, and known pharmacological activities (Kaunda and Zhang, 2019).

Phytochemical group	Total no. of isolated compounds	Plant parts	Pharmacological activities
Steroidal saponins	134	Leaves, whole plant, fruits, aerial parts, and roots	Anticancer, antiviral, anti-inflammatory, anticonvulsant, antifungal, anti-melanogenesis, antihypertensive, hepatoprotective, and cytotoxic
Terpenes*	128	Whole plant, aerial parts, stem, leaves, seeds, fruits, and roots	Anticancer, anti-nociceptive, and antifungal
Flavonoids	75	Whole plant, aerial parts, stem, fruits, seeds, leaves, and roots	Anticancer, antiviral, antidepressant, antioxidant, hepatoprotective
Sterols	66	Seeds, fruits, leaves, and roots	Anticancer, antifungal, anti-plasmodial
Steroidal alkaloids	63	Stem, fruits, whole plant, roots, leaves, aerial parts, and seeds	Antidiabetic, leishmanicidal, schistosomicidal, trypanocidal, anticancer, antibacterial, molluscicidal, antidepressant, anti-inflammatory, neurotoxic, antifungal, spasmolytic, antioxidant
Other alkaloids	31	-	Antimicrobial, antidiabetic
Phenolic compounds	52	Whole plant, aerial parts, stem, fruits, leaves, seeds, and roots	Anticancer, antibacterial, antidiabetic, antihypertensive
Lignans	31	Whole plant, stem, fruits, leaves, seeds, and roots	Anti-inflammatory, anticancer, antifungal, anti-plasmodial, and antidiabetic
Fatty acids and esters	23	-	-
Coumarins**	20	Whole plant, aerial parts, stem, leaves, seeds, fruits, and roots	Anticancer and anti-inflammatory
Pregnane glycosides	13	Whole plant, aerial parts, and fruits	Anticancer
Coumarino-lignoids	4	Seeds	Anti-HBV
Total	640		

Notes: *Total number of terpenes is 128, consisting of 14 triterpenes, 4 diterpenes, 81 sesquiterpenes, and 28 monoterpenes.

**Total number of coumarins is 20, consisting of 17 coumarins and 3 coumastans. HBV: Hepatitis B virus.

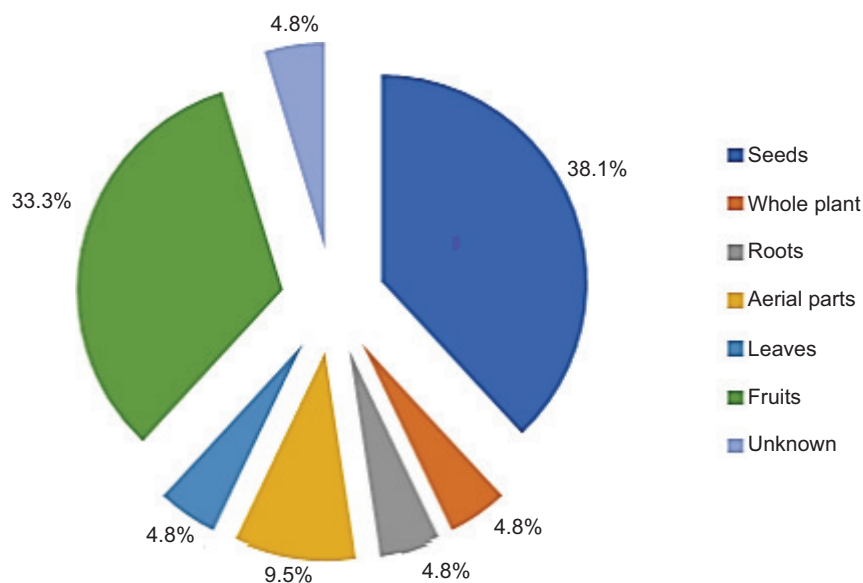


Figure 6. The whole reviewed articles according to the plant parts of *S. dubium* (n = 21 research articles).

Table 5

Summary of the total number of articles on phytochemical compounds isolated from *Solanum dubium*, including their phytochemical groups and plant parts.

No. of articles	Plant part	Phytochemical group	References
1	Whole plant	Steroidal saponins, flavanols	Zhang, 2015
3	Seeds	Chymotrypsin-like serine protease, chymotrypsin a serine-like protease enzyme, ellagic acid, and gallic acid	Abbas and Abdelrahman, 2021; Mohamed et al., 2020; Mohamed Ahmed et al., 2009
1	Aerial parts	Number of phenolic compounds	Qin et al., 2016
1	Leaves	A chalcone molecule	Athar et al., 2021
Total	6		

Table 6

Summary of the total number of articles on the pharmacological activities of *Solanum dubium*, including their associated plant parts.

No. of articles	Plant part	Pharmacological activity
5	Seeds	Toxicological, antibacterial, antifungal, and antioxidant
1	Whole plant	Cytotoxic*
3	Aerial parts	Antifungal, anticancer,** and antibacterial
1	Leaves	Antioxidant
6	Fruits	Anti-schistosomiasis, toxicological, anti-acne, antioxidant, and anti-hyperlipidemic
1	Unknown	Antidiabetic
Total	17	

Notes: *The experiments were conducted by using only hepatic and lung cell lines (*in vitro*).

**The experiments were conducted by using only hepatic and renal cell lines (*in vitro*).

diseases, neurodegenerative diseases, hepatotoxicity, aging diseases, etc. Regarding the anti-proliferative and anticancer properties, the plant was examined *in vitro* by using hepatic, lung, and renal cell lines.

Therefore, very few research articles have tested different plant organs of *S. dubium* for various pharmacological activities. We recognized that only eight pharmacological properties were examined in only five parts of the plant (Table 6). Few articles recommended isolation and structure elucidation of active phytochemical compounds in *S. dubium*. Generally, various plants that belong to the family Solanaceae have demonstrated many pharmacological activities. For example, in the field of anticancer activity, strong cytotoxic and antitumor properties against various cancer cell lines were shown by many plants belonging to the genus Solanum and other Solanaceous plants (Ur Rahman et al., 2014). This antitumor activity primarily was attributable to their steroidal alkaloids, such as

glycoalkaloids, which can inhibit the growth of various cancer cell lines, including liver and colon cancers. These findings emphasize the potential of the Solanaceae family and the genus Solanum in developing cancer treatment, particularly because of their ability to induce apoptosis in cancer cells and herpes viral infection (Fekry et al., 2019; Ikeda et al., 2003). These findings suggest that *S. dubium*, as a member of the genus Solanum, which is rich in phytochemical constituents, may also possess potential antitumor, anticancer, and anti-proliferative properties, as well as potential to combat many other diseases which are difficult to be treated by the modern medicine.

5. CONCLUSION

Solanum dubium (Syn. *S. coagulans*) belongs to the Solanaceae family and is recognized for its various traditional and non-pharmacological applications, particularly its milk-clotting properties and its role in cheese production. This species is rich in alkaloids, flavonoids, tannins, saponins, coumarins, and sterols. These phytochemical groups are abundant in the Solanaceae family, especially the Solanum species. Numerous phytochemical compounds have been isolated and identified from various Solanum species, demonstrating significant pharmacological properties. However, published research on the phytochemical properties and pharmacological uses of *S. dubium* is limited, compared to other Solanum species. Only a few studies have focused on the isolation and identification of phytochemical compounds found in *S. dubium*, primarily identifying phenolic compounds, flavonoids, and steroidal saponins.

Furthermore, most published research has concentrated on the seeds, with very few studies exploring the aerial parts, whole plant, and leaves. This highlights the need for further investigation into the phytochemical composition and potential pharmacological applications of *S. dubium*, because many alkaloids, sterols, and coumarins have numerous

pharmacological properties. In addition, few articles are published on the pharmacological properties of *S. dubium*. The majority of articles focused on antioxidant and antimicrobial activities; others conducted toxicological studies, focusing on cytotoxic, anti-schistosomiasis, antidiabetic, anti-hyperlipidemic and anti-HIV activities, with focus on only the seeds, fruits, whole plant, aerial parts, and leaves.

The plant has demonstrated significant antioxidant activity, through which it could serve as a natural antioxidant aiding in the treatment of many related oxidative stress diseases. Regarding cytotoxic activity, the plant has been only examined, *in vitro*, by using hepatic, lung and renal cell lines. Therefore, additional research is recommended for other pharmacological properties, focusing on all organs of the plant. Moreover, additional works are required in the field of anticancer and other related oxidative stress diseases by using various cell lines, *in vivo* and clinical validations. These studies should attempt bioassay-guided isolation and identification of active phytochemical compounds.

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CONFLICT OF INTEREST

The authors declared no competing interest.

AUTHOR CONTRIBUTIONS

Conceptualization: M.M.; methodology: M.M., A.M.K., F.I.M., and G.K.S.; validation: W.O., M.H.A., A.I.F., A.A., and T.M.A.; formal analysis: M.M., A.M.K., F.I.M., and R.M.S.; investigation: M.M., A.M.K., F.I.M., and G.K.S.; resources: M.M., A.M.K., F.I.M., and G.K.S.; data curation: R.M.S.; writing—original draft preparation: M.M., A.M.K., F.I.M., and G.K.S.; writing—review and editing: W.O., M.H.A., A.I.F., A.A., T.M.A., and R.M.S.; fund acquisition: W.O. All authors had read and agreed to the published version of the manuscript.

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