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Ethnobotanical uses and phytochemical, biological, and toxicological profiles of *Datura metel* L.: A review

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ABSTRACT

Datura metel L., a recognized poisonous plant in the Solanaceae family, is widely distributed in the world. Traditionally, D. metel is used in many diseases, including neurological and heart diseases; fever; catarrh; pain; diarrhea; skin diseases; chronic bronchitis; asthma; digestive disorders; and so on. It possesses many important phytochemicals that can be used to treat various types of diseases. This review aims at summarizing the traditional uses, phytochemical, biological, and toxicological profiles of D. metel based on the database reports. For this, an up-to-date (till March 20, 2023) search was made in the databases: PubMed, Google Scholar, Science Direct, Scopus, and MedLine, with relevant keywords for the published evidence. Findings suggest that the plant has many traditional uses, such as a cure for madness, epilepsy, psoriasis, heart diseases, diarrhea, mad dog bites, indigestion, etc. It possesses various important phytochemicals, including withanolides, daturaolone, datumetine, daturglycosides, ophiobolin A, baimantuoluoline A, and many others. D. metel has many important biological activities, including antioxidant, anti-inflammatory, anti-microbial, insecticidal, anti-cancer, anti-diabetic, analgesic, anti-pyretic, neurological, contraceptive, and wound healing capacity. In conclusion, the toxic plant, D. metel, can be considered a potential source of phyto-therapeutic lead compounds.

Introduction

In Bengali, the local name of Datura (Datura metel L.) is “Dhutura-ধুতুরা”. Other common names are in Arabic: tatura, jozmashel, jozmathel; in Chinese: yang jinhua; in English: purple thorn-apple, downy thorn-apple, Hindu datura, hoary thorn-apple, Hindu thorn-apple, horn-of-plenty; in Hindi: sadadhatura; in Korean: huindogmalpul; in Portuguese: burbiaca; in Spanish: burladora; in Sweden: indisk spikklubba (Al-Snafi, 2017a). The genus *Datura* (Family: Solanaceae) can be found throughout the world, and there are 14 species, among these, ten species are available in India. Compared with other species, *D. metel*, *D. innoxia*, and *D. stramonium* are the most significant medicinal plants (Schultes and Hofmann, 1979).

D. metel is a perennial plant. The structure of leaves is simple: alternate, dark green, shallowly lobed, and broadly ovate. The appearance of flowers is large, single, and trumpet- growth, extending branches, and an herbaceous plant of about 1.5 m height. The structure of leaves is simple: alternate, dark green, shallowly lobed, and broadly ovate. The appearance of flowers is large, single, and trumpet-shaped, with a pleasant fragrance and various colors; for instance, in some species, they are white to yellow, and in others, they are light to dark purple. The fruit is egg-shaped, capsulated with short spines, and its diameter is 5 cm. However, it is fond of the worm regions of the world (Drake et al., 1996), as taxonomy shows in Fig. 1.

Under the Solanaceae family, there is evidence of 9–14 species of the Datura genus, but not every species has significant distinction to identify it, so only 9 species are widely acceptable; those are *D. ceratocaula* Ortega, *D. discolor* Bernh, *D. ferox* L., *D. innoxia* Mil, *D. kymatocarpa* Barclay, *D. leichhardtii* Benth, *D. metel* L., *D. quercifolia* Kunth, *D. stramonium* L., and *D. wrightii* Regel. *D. metel* is available in Asian and African region (Preissel and Preissel, 2002). Different parts of *D. metel* are shown in Fig. 2.

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D. metel contains a lot of significant phytochemicals, including alkaloids, flavonoids, tannins, phenols, cardiac glycosides, amino acids, and carbohydrates (Al-Snafi, 2017b). Various parts of the herb are being utilized as hallucinogenic, narcotic, anti-tussive, antispasmodic, bronchodilator, and anti-asthmatic and are used in epilepsy, diarrhea, hysteria, skin diseases, rheumatic pains, painful menstruation, hemorrhoids, wounds, burns, and skin ulcers. *D. metel* is considered an astringent, bitter, germicide, acrid, anti-phlogistic, anodyne, narcotic, antiseptic, and sedative medicinal plant in Ayurveda (the Ayurvedic Pharmacopoeia of India). Haploid embryos were also developed by Anther culture to produce a haploid *D. metel* plant (Wijesekara and Iqbal, 2021). This review summarizes the phytochemical reports and biological activities of *D. metel* on the basis of database reports.

Results and discussion

Database reports

The latest (till March 20, 2023) searching was performed in the databases: Google Scholar, PubMed, MedLine, Science Direct, and Scopus, with the keywords "Datura metel" and/or paired with "ethno-botanical use", "phytochemicals", and "pharmacological activities". There were no language restrictions. By searching, we have yielded 823 references. From there, 69.99% of the articles were removed for being duplicated throughout the databases; 8.75% were removed for being ineligible by automation tools; 121 articles, or 14.70%, were screened, where 28 articles were excluded for insufficient information; then 76 articles were assessed for eligibility, where 12 articles were excluded for three reasons; and finally, this study included 66 new articles for the review. The PRISMA analysis for data inclusion is shown in Fig. 3.

Traditional uses

Information regarding the traditional uses of natural products and their derivatives has played pivotal roles in the discovery and development of therapeutic agents since ancient times (Pirintsos et al., 2022). Traditionally, D. metel is used to treat epilepsy along with skin diseases, hysteria, fever with catarrh, insanity, heart diseases, and diarrhea. For pain relief, the leaves are used. For treating asthma, this plant is used in China and Vietnam. D. metel plant extract is also used as general anesthesia and in the treatment of chronic bronchitis (Ko and Ko, 1999; Kam and Liew, 2002). D. metel is also used traditionally in India as a cure for madness or insanity, cerebral complaints and catarrhal infections, elephantiasis, ear discharge, skin diseases, mad dog bites, and indigestion (Tripathi et al., 1996). The flower of D. metel is called biamantuoluo in Chinese traditional medicine, where it is mentioned as useful for skin inflammation and psoriasis (Wang et al., 2008). Seeds of D. metel are used as an ingredient in tea in Brazil, which provides a sedative effect, and dried flowers of the plant are used for smoking (Monira and Munan, 2012). Young Nigerians also consider D. metel as a hallucinogenic agent (Ishola et al., 2021).

In Bangladesh, different parts of the D. metel plant are utilized in the treatment of scabies, eczema, and allergies (Ishola et al., 2021), abnormal breathing, pupil problems, pain and swelling, breast pain, asthma, convulsions, and rheumatism (Rahmatullah et al., 2010).

Phytochemical profile

Plant-derived constituents are one of the potential sources of therapeutic bioactives, thus modern medicines. Many important therapeutic medicinal strategies, for example, the basis of therapy of Traditional Chinese medicine (TCM) is composed of natural products and their derivatives, in which phytochemicals are the major candidates (Xiang et al., 2019). Medicinal plants and their isolated compounds are used widely to treat many maladies. Approximately 35% of modern medicine originates from natural sources (Calixto, 2019). D. metel has an important place in the traditional systems of medicine as a narcotic, anodyne, and antispasmodic drug similar to Belladonna and Stramonium. Withanolides, tropane alkaloids, and steroidal lactones have been reported from D. metel. The plant contains β-sitosterol (Han et al., 2015). D. metel also contains many important alkaloids, including littorine, hyoscyamine, acetoxytropine, hyoscine, fastusine, valtropine, and fastusinine, along with different withanolides, tropine (trigloyl esters), and pseudo-tropine. These are presented in Table 1. However, glycosidase inhibitory activity has been found in the nortropane alkaloids, calystegines, isolated from various species of D. metel (Ghani,

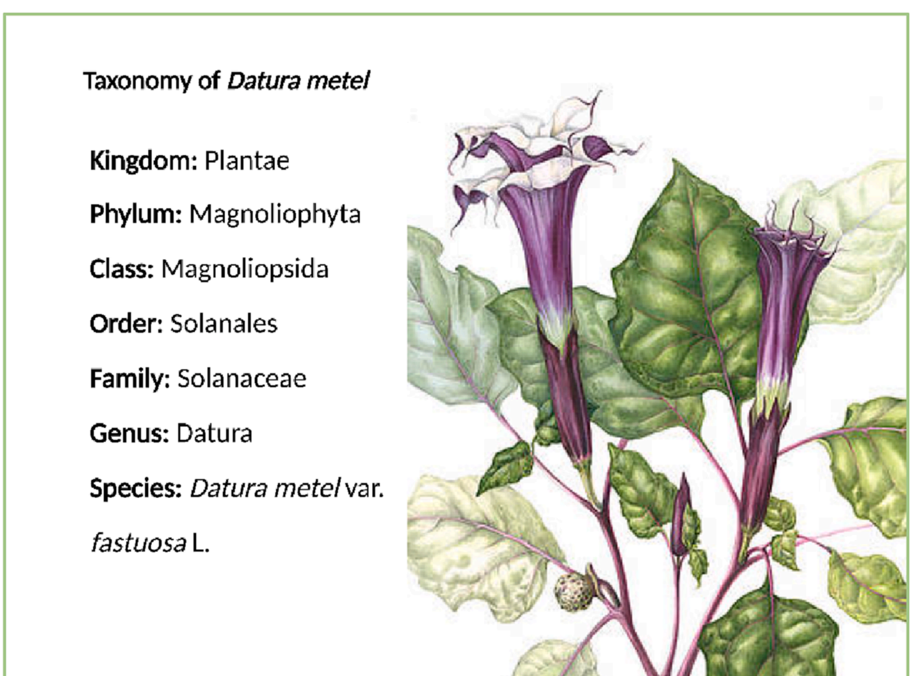

Fig. 1. Taxonomy of *Datura metel.*

2003). The root of D. metel is rich in atropine, while the aerial parts are rich in scopolamine (Afsharypuor et al., 1995).

Five metelosides A–E and four known compounds were isolated from an acidic methanol whole plant extract of D. metel. Cytotoxic effects have been shown for 4, 5, 6, and 2 compounds on MCF-7, SK-Mel-2, and HepG2 cells. On the other hand, three compounds (3, 4, and 7) also moderately showed anti-inflammatory action by suppressing nitric oxide (NO) generation in BV cells, which was stimulated by lipopolysaccharide (LPS)-stimulated (Mai et al., 2017a). Seven glycosides (daturglycosides 1–7) have been isolated from D. metel leaves (Tan et al., 2021), as shown in Fig. 4.

Three new compounds (sesquiterpenoid and aliphatic glycoside) have been isolated from D. metel roots 70% ethanolic extract, along with 36 known compounds; among these compounds, authors have found that 5 show strong anti-inflammatory activity (Liu et al., 2021). A new compound, phenolic glycoside (methyl 3,4-dihydroxyphenylacetate-4-O-[2-O-β-D-apisoyl-6-O-(2-hydroxybenzoyl)]-β-D-glucopyranoside) is isolated from roots (Qin et al., 2021). Major bioactive compounds are presented in Table 2.

Bioactivities of Datura metel

Table 2 reports the diverse biological activities of *D. melel*. Each biological effect has been described in the table.

Antioxidant activity

Oxidative stress leading to inflammatory responses is one of the major defense networks in mammals. However, chronic oxidative stress or inflammation may initiate and progress a variety of diseases (Dandekar et al., 2015). D. metel and its derived compounds have been evidently exerting antioxidant (Akharaiyi, 2011; Bhardwaj et al., 2016) and anti-inflammatory effects (Yang et al., 2017) in some studies. A substance having antioxidant and/or anti-inflammatory activity may protect organs, including the nervous system (Islam et al., 2016). The ethanolic and aqueous extractions of the plant showed a significant DPPH radical scavenging capacity between 25.51 and 3.41% and 49.30 and 23.82%, respectively (Akharaiyi, 2011). In this study, a phytochemical report suggests that crude ethanol and water extracts of the different parts of the herb contain alkaloids, saponins, glycocides, phenols, and flavonoids. The antioxidant capacity of D. metel has also been seen by Bhardwaj et al. (2016).

However, in the DPPH model, hydroalcoholic extract of seed showed slightly higher antioxidant action than the methanolic extract, that is hydroalcoholic IC_{50} value was 25.78 μg/mL and methanolic extract of seed's IC_{50} value was 28.34 μg/mL (Alam et al., 2020; Al-Snafi, 2017a). Importantly, compared with other species like D. stramonium, D. metel's antioxidant property is quite high (Iqbal et al., 2017). Antioxidant action is estimated by the aqueous extract of seed and leaf of D. metel at 2.5 and 1.5 mg/mL, respectively; they also found that it prolongs the cardiac arrest to 35 to 37 min, when the heart's normal survival time is 14 min (Mbida et al., 2022). Four extract concentrations of four different solvents of D. metel extract 25–100 mg/mL were investigated in DPPH scavenging activity, total phenolic content, the reducing power assay, hydroxyl-radical scavenging, and β-carotene bleaching test. The results showed concentration-dependent antioxidant activity; the higher the concentration, the greater the effect (Sangeetha et al., 2014). In another study, the n-hexane extract contained tocopherols, of which 80% were gama-tocopherol, and this n-hexane extract had the ability to extinguish 40% of the DPPH radical (Ramadan et al., 2007). CeO_2 nanoparticles prepared with D. metel ethanolic extract CcO_2 NPs have found DPPH radical scavenging of 16.61% (Yulizar et al., 2020).

Anti-inflammatory and immunomodulatory effects

A unani drug for asthma named Habb-e-Zeequn Nafas (HZN), where D. metel is used as the active ingredient, was found to be safer in preclinical tests (Firdaus et al., 2022). A newly isolated glycoside from D. metel roots (methyl 3,4-dihydroxyphenylacetate-4-O-[2-O-β-D-apisoyl-6-O-(2-hydroxybenzoyl)]-β-D-glucopyranoside) has anti-inflammatory activity (Qin et al., 2021). D. metel leaf, seed, and fruit extracts were tested on male albino rats and found to have a nephroprotective effect on kidney function (Imo et al., 2019). Withanolides were found effective against psoriasis, and the mechanism was also established (Cheng et al., 2020). A new drug named 'D. metel L. capsule," which was approved for treatment and showed more than 90% efficacy and 65% cure rates (Su et al., 2022). Successful Cu_2O nanoparticles were prepared by using D. metel extract, but their effect was not determined (Chinnaiah et al.,

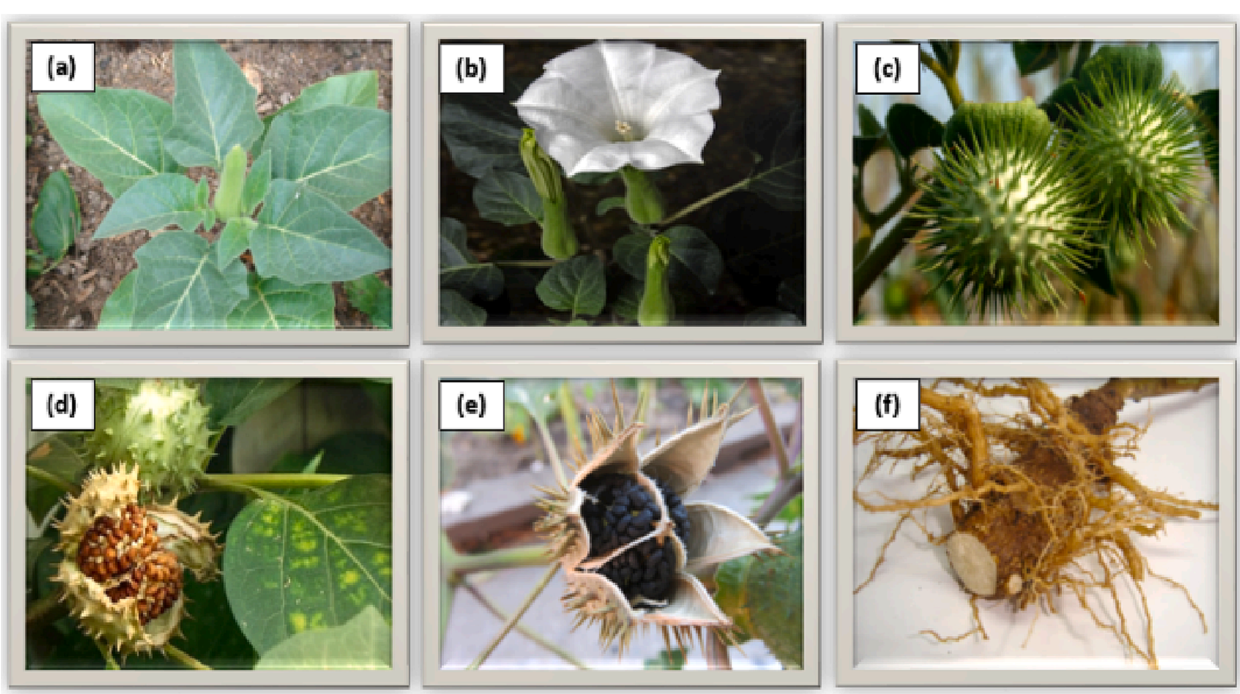

Fig. 2. Different parts of *Datura metel* [(**a**) plant, (**b**) flower, (**c**) unripe green fruits, (**d**) ripe canary fruits, (**e**) mature black-seeds, (**f**) roots of *D. metel*].

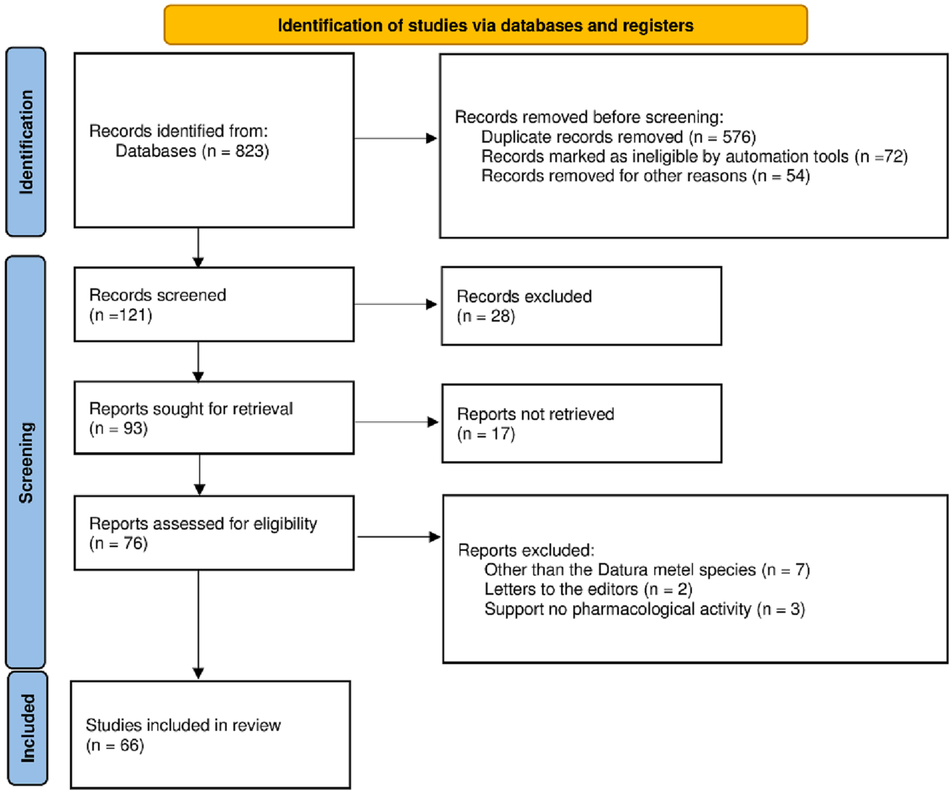

Fig. 3. PRISMA analysis of database reports for *Datura metel.*

Table 1
Constituents of alkaloids of *Datura metel.*

D. metel parts	Alkaloidal presence (%)	Major constituents	Sources
Leaves	0.426%	Hyoscyamine, scopolamine and atropine, withanolides	Siddiqui et al., 1987; Dabur et al., 2005
Roots	0.35%	3α-tigloyloxytropane, hyoscine, hyoscyamine, norhyoscine, tropine, apohyoscine, tigloidine and cuscohygrine	Ghani, 2003
Seeds	0.426%	Daturanolone, hyoscyamine and fastusic acid and some tropane alkaloids	
Fruits (Pericarp)	Not quantified	Daturanolone, β-sitosterol, daturadiol, and tri-terpene	
Seeds	Not quantified	4 new indole alkaloids daturametelindoles A-D (1–4)	Liu et al., 2020
Propagated shoots	Not quantified	withanolide-12-deoxywithastramonolide and C28 sterol 3β,24ξ-dihydroxy-ergosta-5, 25-dienolide compounds	De, 2003
Cultured callus	Not quantified	5α-pregnane3β,20β-diol and Cholesterol compound	
Flowers	Not quantified	5 compounds of withanolide (baimantuoluoline **A-C** and withametelin **C** and withafastuosin **E**), withametelins 10 compounds **I-P**, and 12β-hydroxy-1,10-seco-withametelin **B** and 1,10seco-withametelin **B** compounds.	Agharkar, 1991; Manickam et al., 1993; Yang et al., 2010a

2022).

Anti-microbial activity

Anti-bacterial effect

Anti-bacterial activity is a very intricate process that involves microscopic creatures whose ability to reproduce and function at every stage of life, including nourishment, metabolism, and respiration, can be impacted by the presence of potentially harmful elements (Patachia and Croitoru, 2016). A zone of inhibition is a region of media in which bacteria are unable to grow due to the presence of a medication that inhibits their growth. The lowest inhibitory concentration of an anti-microbial medication that precludes observable growth of a bacterium after overnight incubation with medium (Barnard, 2019).

The ethanolic and aqueous extracts (20 mg/mL) of leaf, stem bark and roots of *Datura* acted against*, Streptococcus dysenteriae* (gram-negative)*, Pseudomonas aeruginosa* (gram-negative), *Bacillus cereus* (gram-positive), *Escherichia coli* (gram-negative), *Klebsiella pneumoniae* (gram-negative)*, Staphylococcus aureus* (gram-positive)*, and Streptococcus* β *hemolytic* (gram-positive*)* (Akharaiyi, 2011). In this study, the leaves and stem bark extracts produced zones of inhibition between 12 and 35 mm, while the aqueous extract by 10 to 22 mm, and by ethanol extract 12 to 32 mm. The MBC was 10 to 20 mg/mL. So, *D. metel* has inhibitory action against both of the gram-positive and gram-negative strain and *S. aureus* was the mostly suppressed bacteria by the ethanolic extract.

According to Bachheti et al. (2018), at least 7 bacterial strains showed the highest inhibition zone and lowest MIC when treated with the seed oil, including Pseudomonas aeruginosa (18 mm) and Lactobacillus delbrueckii lactis (19 mm). Studies have shown that the higher the oil concentration, the greater the antibacterial response. Methanolic extract depicted ($p < 0.05$) antibacterial effect and biofilm inhibition against Bacillus subtilis, MRSA, and E. coli at 94, 88, and 92%, respectively (Prasathkumar et al., 2022). Silver nanoparticles (25–70 nm) were

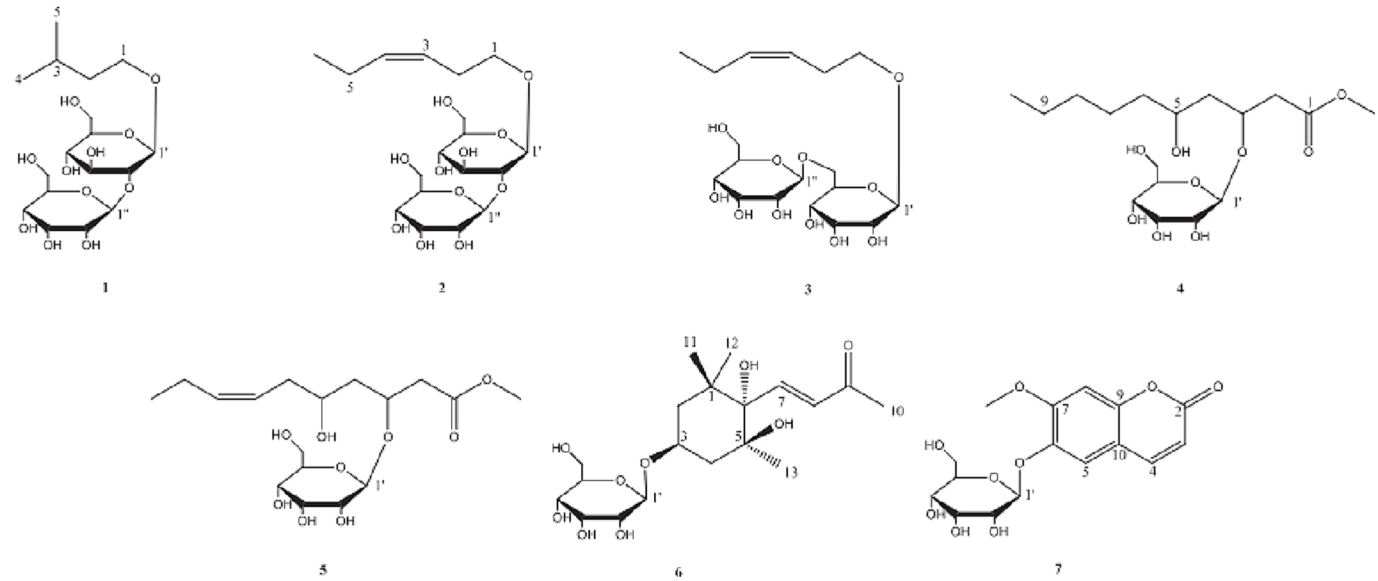

Fig. 4. Newly isolated seven daturglycosides (**1**–**7**).

prepared in D. metel extract with ultrasound and found to have a higher zone of inhibition on tested bacteria (Nethradevi et al., 2012; Fatimah et al., 2021).

Anti-fungal effect

In a study, the chloroform, hexane, methanolic, and acetone fractions of D. metel were found to act against Aspergillus fumigatus, A. niger, and A. flavus (Rajesh and Sharma, 2002). The minimum inhibitory concentration found for the chloroform solvent was 625.0 μg/mL. A derivative of pyrrole, named- 2β-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl)-10-methylethyl pentanoate, separated from the leaf of the plant, was found to act against A. niger, Candida albicans, A. flavus, C. tropicalis, and Aspergillus fumigatus (MIC value: 87.5 mg/mL) (Dabur et al., 2004). In a disc diffusion assay, the MIC was observed at 12.5 mg disc, and the methanol extract of D. metel was investigated against the Aspergilli, and the MIC was observed 1.25–2.50 mg/ml (Dabur et al., 2004; Monira and Munan, 2012). D. metel extract of leaves and stem showed antifungal properties; these authors used 6 methanol concentrations (1, 1.5, 2, 2.5, 3, and 3.5%), and found leaf 3.5% conc. has ability to inhibit Rizoctonia solani Kuhn at 75%, which is greater than stem at same concentration (Hanif et al., 2022).

Anti-viral effect

An atropine isolated from the Datura inhibited the growth of enveloped viruses (e.g., HBV, HCV, HIV, and influenza viruses) and also inhibited the glycosylation of viral proteins of the Herpes virus, resulting in no formation of virions (Yamazaki and Tagaya, 1980). Effective against tomato mosaic virus (TMV), activated oxygen species play the defensive role against the virus and program cell death to save the plant from this virus (Al-Huqail and Aref, 2017).

Wound healing activity

The process of returning damaged tissue's tissue structure to its pre-injury state as closely as feasible is known as wound healing. Its characteristics include coagulation factors, inflammatory processes, re-epithelialization, granulation, modification of the extracellular matrix, and scarring (Boakye et al., 2018). It is reported that the seed of D. metel is externally used for piles (Yusuf et al., 1994; Yusuf et al., 2009). Datura ointment at 10% w/w, in an excision wound model, exhibited significant wound healing capacity in Wistar albino rats. The result was comparable to the standard, nitofurazone 0.2% w/w, which was used in this study (Vimal and Suseela, 2010).

Studies have found that pre-ingestion of seed extract of Datura increased the viable rate of the rat after toxication with dichlorvos; the possible reason could be the availability of a significant percent of atropine in seeds and other anticholinergic compounds in it (Das et al., 2012; Manpreet et al., 2017). Providing D. metel seed extract 7.5 mg/kg intraperitoneal injection to male rats before giving 25 mg/kg dichlorvos inj. showed longer times of survival, even 24 h more survival in the case of Datura-treated animals (Bania et al., 2004; Al-Snafi, 2017a). The wound-healing capacity of D. metel and its isolated compounds confirm the medicinal value of this plant (Vimal and Suseela, 2010).

Herbicidal activity

A weed-killer or herbicidal compound is a substance used to kill plants, particularly weeds or other undesirable species (Almarie, 2022). The n-hexane, methanol, and water extracts of root and shoot at 5, 10, and 15% (w/v) of the plant exerted noticeable herbicidal action on Phalaris minor Retz. Moreover, the methanol (5–15%) and n-hexane (15%) root extracts of this plant also considerably lowered the germination, shoot, and root lengths of the sample (Javaid et al., 2008).

Insecticidal activity

The methanolic extract of Datura seeds at 2.5, 5.0, 7.5, and 10.0% were found to act against Helicoverpa armigera (Hubner) (Singh and Singh, 2008). This study was also supported by the authors Monira and Munan (2012) and Al-Snafi (2017a), who said methanolic extract of D. metel seeds significantly blocked different developmental stages such as larval, pupal, pupation quantity, and adult emergence.

Anti-cancer activity

Different glycosidases are effectively inhibited by nitrogen-rich polyhydroxylated compounds. They can be utilized for treating many diseases, including cancer, diabetes, immunological diseases, and virus-causing infections (Wang et al., 2019). Including Datura, other 14 Solanaceae family plants contain a significant number of withanolides, and these compounds have a notable anti-cancer effect by creating oxidative stress and downregulating NF-kB, transcription factor STAT3, and Hsp90. The inhibition of PI3K/Akt and MAPK pathways results in cytoskeletal and structural protein dysregulation. Cancer cell angiogenesis is inhibited via HIF-1 downregulation (Akhtar et al., 2020; Nkwe et al., 2021), a possible anticancer pathway depicted in Fig. 5. Withanolides have lots of significant biological activities, for example, anti-tumor activity (Bellila et al., 2011), and importantly, anti-

Table 2
Bioactivities of phytoconstituents of *Datura metel.*

Compounds name	Parts/derivatives	Extraction process	Result/activity	References
Withafastuosin	Flower	70% Ethanol used	Depicted activity for psoriasis	Yang et al., 2007
Two new lignin compounds, Compound 1 ($C_{21}H_{22}O_7$), compound 2 ($C_{27}H_{32}O_{12}$) and known 18 lignin compounds	Roots	70% Ethanol	Cytotoxicity test against Hela cell line IC_{50} for compound 1 (48.20 μM) and for compound 2 (58.86 μM)	Yang et al., 2018
Withametelins	Flower	Methanolic extraction	Cytotoxicity showed	Pan et al, 2007
Sesquiterpenoids, nine new (1–9) and three known (10–12)	Leaves	Ethanol extract ethanol–water (7:3, v/v)	Anti-inflammatory activity against RAW264.7 and IC_{50} value was 9.33–11.67 μM, control group was greater thana this.	Tan et al., 2020a
Withanolides	Flower	Used 50% Ethanol	Presented activity for psoriasis	Yang et al., 2007
Ophiobolin A	Produced by its endophytic fungus (*Bipolaris* sp.)	–	Anti-cancer activity	Maehara et al., 2020
Baimantuoluoline A	Flower	50% Ethanol	Showed the activity for psoriasis	Yang et al., 2007
(5α,6β,7α,22R)-5,6,7,27-tetrahydroxy-1-oxowitha-2,24-dien-27-O-β-D-glucopyranoside	Flower	Extracted with 70% Ethanol	For treating of psoriasis	Yang et al. (2010b)
6,7-dimethyl-1-D-ribityl-quinoxaline-2,3(1H,4H) - dione-5′-O-β-Dglucopyranoside	Flower	Used 70% Ethanol	Psoriasis treatment	Yang et al. (2010b)
Sesquiterpenoid and aliphatic glycoside	Roots	70% Ethanol	Anti-inflammatory activity by 5 compounds	Liu et al., 2022
(E)-methyl 4-(3-(4hydroxyphenyl) -N- methylacrylamido) butanoate	Flower	70% Ethanol used for extraction	Treatment of psoriasis	Yang et al., 2010a
Ergostane-type C28 sterols, daturmetesides A-E (1–5)	Leaves	70% Ethanol	Anti-inflammatory activity, IC_{50} values ranging from 17.05 ± 0.35 μM to 24.88 ± 0.93.	Tan et al., 2020b
1, 10-seco-withametelin B	Flower	Methanolic extraction	Cytotoxicity is observed	Pan et al., 2007
12 β -hydroxy-1,10-seco-withametelin B	Flower	Methanolic extraction	Cytotoxicity is observed	Pan et al., 2007
Alkaloid datumetine	Leaves	Para-methoxy benzoic acid	Anti-spasmodic action	Siddiqui et al., 1987
Lignin-amides from Datura metel seeds (LDS)	Seeds	95% Ethanol	Anti-neuroinflammatory, Alzheimer disorder	Wang et al., 2021
2-(3,4-dimethyl-2,5-dihydro-1H-pyrrol-2-yl) -1- methylethyl pentanoate	Leaves	Chloroform	Antifungal activity, MIC 87.5 μg/ml	Dabur et al, 2005
Melatonin	Flower	Methanolic extract	Cold stress controlling	Murch et al., 2009
Serotonin	Flower	Methanolic extract	Induced during stress-condition	Murch et al., 2009
2 new compounds- meteloside F(1) and meteloside G(2) and 6 known steroids	Seeds	95% Ethanol	Inhibiting nitric oxide production from RAW 264.7 cells, IC_{50} value 30.2–44.8 μM	Yang et al., 2020
Seven new glycoside and seventeen known	Leaves	70% Aqueous ethanol	Antiproliferative activity to MGC-803, Hela, and Ishikawa cell-lines	Tan et al., 2021
A phenolic glycoside name- methyl 3,4-dihydroxyphenylacetate-4-O-[2-O-β-D-apisoyl-6-O-(2-hydroxybenzoyl)]-β-D-glucopyranoside	Roots	Ethanol	Anti-inflammatory activity	Qin et al., 2021
Found Alkaloid (88.77 ± 1.01 mg AE/g), Phenolic (124.61 ± 0.68 mg GAE/g), tannins (38.72 ± 0.51 mg GAE/g), flavonoids (42.24 ± 0.18 mg QE/g)	Leaves	Methanol	Antibacterial, anti-diabetic, antioxidant, anti-inflammatory, cytotoxic effects etc.	Prasathkumar et al., 2022
13 new withanolide aglycones, baimantuoluolines L-X, with baimantuoluoside J (a new withanolide glycoside)	Flowers	Ethanol	Immunosuppressive by 1–14 compounds and anti-proliferative action against SGC-7901, HepG2, MCF-7were tested.	Liu et al. (2020a)
12 undescribed withanolides	Leaves	Ethanol	Inhibits nitric oxide production, IC_{50} value for daturafoliside L, T, M ranging from 9.37 to 18.64 μM and for K, R, A range 22.84–33.36 μM	Guo et al., 2018
2 guainane sesquiterpenes, (1)1β,5α,7β-guaiane-4β,10α,11-triol and (2)1α,5α,7α-11-guaiene-2α,3β,4α,10α,13-pentaol, along with 8 described compounds	Whole plant	Methanol	Anti-inflammatory effect was ensured by NO inhibition.	Mai et al., 2017
Daturaolone	Fruits	Chloroform	Potent anti-fungal and antibacterial action. Effective against *B. subtilis, Klebsiella pneumonia, S. epidemidis, S. aureus* and zone of inhibition found 12–30 mm. Moreover, fruit extract provide modest sensitivity	Bawazeer, and Rauf, 2021

(*continued on next page*)

Table 2 (*continued*)

Compounds name	Parts/derivatives	Extraction process	Result/activity	References
			against *C. glabrata, T. longifusus, F. solani, C. albicans, M. canis, A. flavus*	
Daturataturin A (DTA)	Dried Flowers of *D. metel*	Ethanol	Anti-inflammatory and anti-proliferative effect and anti-psoriasis by activation of autophagy.	Wei et al., 2021
6 known terpenoids (2–6) and a new-diterpenoid called-kaurane daturoside A(1)	Dried pericarps	Ethanol	Compounds 2 and 5 showed anti-inflammatory action against LPS induced RAW264.7 cells (IC_{50} value is lower than 11 μM).	Liu et al., 2021a
12 phyto constituents including (tetradecanoic acids, eugenol, dodecanoic, 2-pentadecanone 6,10,14 trimethyl, 9, 12 octadecanoic acid, pentadecanoic acid, pentadecanoic acid, 6-octadecanoic acid, 1 4-methyl- methyl ester, n-hexadecanoic, 9,12,15-octa-decatrienoic acid, phytol and heptacosane)	Leaves and stem	Methanol	Antifungal effects	Hanif et al., 2022
A total of ten substances, including scopatone, isofraxidin, daturadiol, arenarine D, 1–4-benzenediol, vanillin, G-sitosterol, N-*trans*-feruloyl-tyramine, scopoletin, and hyoscyamilactol	Seed extract	–	–	Han et al., 2015

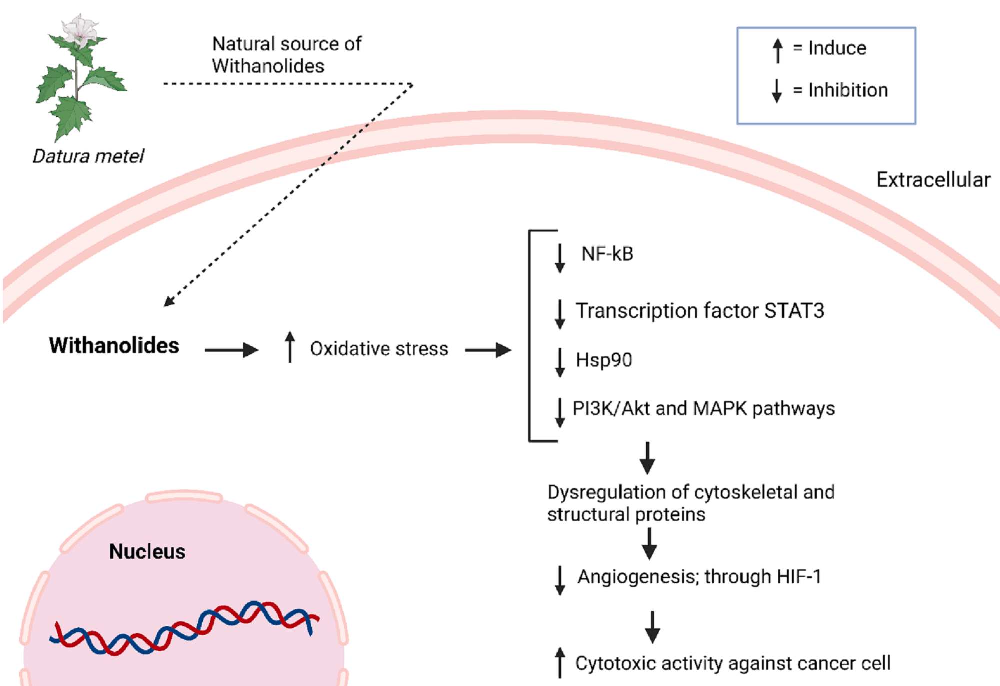

Fig. 5. Possible anticancer mechanism of withanolides (Here withanolides increase oxidative stress and downregulating nuclear factor kappa light chain B (NF-kB), transcription factor signal transducer and activator of transcription 3 (STAT3), heat-shock protein 90 (Hsp90) via phosphoinositide 3-kinase (PI3K)/protein kinase B (Akt) and mitogen-activated protein kinase (MAPK) pathways which results cytoskeletal and structural protein dysregulation; thus, decrease angiogenesis and increase cytotoxic activity against cancer cell).

inflammatory and immunomodulatory effects (Yu et al., 2017). The withanolides have inhibitory effects on tumor cell proliferation, and they can act as angiostatic agents. Moreover, they may induce the phase-II enzyme quinone reductase (Pan et al., 2007).

Datura is evidently a source of calystegines. Some withanolide glycosides (aturametelins), daturataturin, 7,27-dihydroxy-1-oxo and 2,5,24-trienolide are also separated from the methanol extraction process of D. metel aerial parts. The non-glycosidic compound of the plant exhibited a significant antiproliferative effect on the HCT-116 cell line (IC_{50}: 3.2 ± 0.2 μM) (Monira and Munan, 2012). In another study, daturanolides A–C, along with 6 previously described withanolides (4–9), were found in the flowers of D. metel (Wang et al., 2019), as shown in Fig. 6. In this study, compound 6 exhibited marked cytotoxic effects on five human cancer cell lines, such as HepG2, NCI-H460, HCT116, BGC823, and U87-MG. When NF-kB is inhibited, the genes are downregulated, which prevents cancer cells from proliferating and forming new blood vessels. Apoptosis induction in cancer cells may be aided by blocking the NF-kB signaling pathway as well as TNF-related apoptosis-inducing ligands (Varma et al., 2011).

The sesquiterpenoid glycosides, citroside A, dmetelisproside A, and staphylionoside D, separated from the D. metel leaves (Fig. 6), were evaluated for cytotoxic effects towards MDAMB-231, SGC-7901, HeLa, Hepg2, and MCF-7 cancer cell lines, and anti-inflammatory activity was observed on the RAW 264.7 cells. Dmetelisproside A and citroside A showed strong cytotoxicity against HeLa and SGC-7901 cells (IC_{50}: 21.43–29.51 μM). Staphylionoside D, citroside A, dmetelisproside A, and citroside A also inhibited nitric oxide production, with IC_{50} values of 44.31, 34.25, and 31.10 μM, respectively (Guo et al., 2019). Another study have found 3 newly glycosides named- daturametelins **H** to **J** they have tested with other two stablished compound daturataturin-A and 7, 27-dihydroxy-1-oxowitha-2,5,24-trienolide against HCT-116 (human colorectal carcinoma) and have found the IC_{50} values 3.2 ± 0.2 μM.

According to the studies of Al-Snafi (2017b) and Ibrahim et al. (2018), the stem and root extracts of D. metel have demonstrated cytotoxic actions against HepG-2 (human liver cancer cells), where IC_{50} values were 341.12 and 613.88 μg/mL, respectively. On the other hand, the root and leaf extracts were effective against HeLa (cervical carcinoma cells) with IC_{50} values of 348.35 and 267.76 μg/mL, respectively.

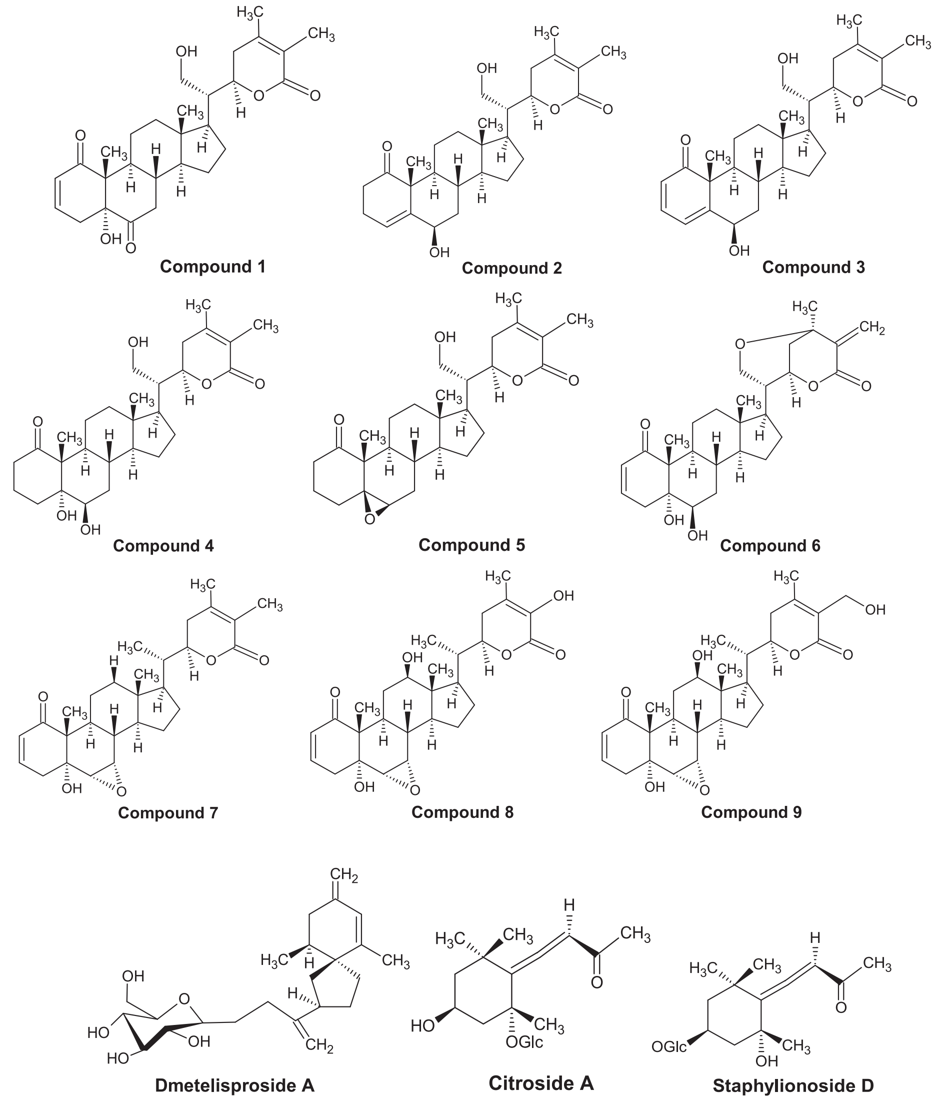

Fig. 6. Chemical structure of some potential anticancer compounds of *Datura metel*.

The IC_{50} of methanolic extraction of D. metel fruits towards the Vero-cell line was found to be 3 mg/mL; in this study, the 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) method was utilized in an in vitro cytotoxicity assay in the Vero-cell line (Roy et al., 2016). Tan et al. (2020a) have evaluated 24 compounds of D. metel against Hela, Ishikawa, and MGC-803 cell lines and found seven compounds provided antiproliferative action.

Hypoglycemic effect

Hypoglycemia is the state of having blood sugar (glucose) levels that are below normal. The body uses glucose as its main source of energy. Diabetes treatment frequently involves managing hypoglycemia (Wild et al., 2007). D. metel seed extract showed hypoglycemic action in alloxan-stimulated diabetic rats (Krishna Murthy et al., 2004). The authors demonstrated that a rapid normalization of blood glucose levels was also seen, possibly due to the increase in protection and secretion of insulin's capabilities by the β-cells.

Neuroprotective effects

Neuroprotection means the processes and tactics used to guard the central nervous system (CNS) against injury caused by both acute (e.g., trauma or stroke) and chronic (e.g., dementia, Parkinson's, Alzheimer's, seizures, etc.) neurodegenerative illnesses (Rehman et al., 2019). In a study, a methanolic crude extract of D. metel at 0.6, 1.2, 1.5, 2, and 2.4 g/kg demonstrated a dose-dependent oral anesthesia in dogs (Babalola et al., 2013). The aqueous extracts of seed and leaf of D. metel are also evident to show neuropsychopharmacological effects in rat and mouse models (Abena and Miguel, 2004). In a study, the aqua extract of D. metel seed at 400 and 800 mg/kg was found to increase nuron-motor activity while lowering the duration of barbituric acid-induced sleeping time, antagonizing catalepsy and inducing ptosis by haloperidol, and inducing immobility in the test animals (Al-Snafi, 2017a). Importantly, NMDAR is a glutamate receptor and ion channel that can be noticed in neurons and is affected by datumetine (the active compound of D. metel) and results in intoxication and memory deficit (Ishola et al., 2021).

Anti-nociceptive effect

The drugs known as analgesics are used to treat pain. Analgesics don't cut off nerves, impair your ability to detect your surroundings, or affect consciousness, unlike the drugs used as anesthetics during surgery. They are referred to as painkillers or pain relievers occasionally (Price, 1999). The aqueous seed extraction of Datura metel did not exhibit analgesic effects on experimental animals (Wannang et al., 2009). However, the alcoholic seed extract exerted a dose-dependent analgesic effect; the ED_{50} was 25 for aqueous seed extraction and 50 mg/kg for the alcoholic extract in the hot plate and formalin tests applied on rats (Khalili and Atyabi, 2004). In a study indomethacin was used as standard drug and compared the result of ethanolic root extract of D. metel in rat and result showed anti-inflammatory activity at 200 mg/kg, comparing Indomethacin (10 mg/kg). On the other hand, an aquas extract of D. metel seeds and leaves was found effective at 800 and 400 mg/kg dosage in mice, and inflammation was induced by acetic acid (Al-Snafi, 2017).

Daturaolone is a potential compound found in D. metel; in a study, it was found that this compound can inhibit cyclooxygenase and lipoxygenase to provide anti-inflammatory and analgesic activity (Rauf et al., 2016); the basic mechanism is to inhibit cyclooxygenase COX-1 and COX-2 and lipoxygenase; this inhibition causes the suppression of prostaglandin synthesis or might be the narcotic effects of Datura species (Chandan et al., 2021; Jaafar et al., 2018). In the process of inflammation, arachidonic acid is crucial because it serves as a building block for the creation of two different types of vital compounds, prostaglandins and leukotrienes, in the body, and daturaolone inhibits the production of prostaglandins and leukotrienes by cyclooxygenase 1 and 2 and lipoxygenase inhibition (Samuelsson, 1987; Baig et al., 2021), as shown in Fig. 7.

Contraceptive effects

Antifertility medications are chemical compounds that block the activity of hormones that encourage pregnancy. These medicines serve as a form of protection and actually lower the likelihood of pregnancy (Rivera et al., 1999). Usually, antifertility medications are derived from synthetic progesterone derivatives or a mix of progesterone and estrogen derivatives (Druckmann, 2009). Plant sources can act as contraceptives or antifertility agents (Brondegaard, 1973) Contraceptive action of D. metel is considerably observed in albino mouse trial by the acetone extracts of seeds, where three concentrations were used (0.5%, 1% and 2%) orally given to female albino. These mice were given the opportunity to mate after 15 days of treatment with normal male albinos. Dissection was performed after ten days and it was found that 2% seed extract showed full (100%) anti-fertilization, whereas 0.5% and 1% seed extracts presented 80% and 40% anti-pregnant action, respectively. This author has commented that D. metel is a good source of contraceptive compounds with inconsiderable side effects (Pandiarajan et al., 2012). Not only this, there was another study on male rats where D. fastuolsa's (metel) ethanolic extract was given orally for 7 weeks at 2, 4, and 6 mg/kg concentration, and the results were surprising as it decreased sperm content and normal sperm compared with the control group. Moreover, hormonal levels of testosterone, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and testicle weight also decreased; as a result, pregnancy occurrence also decreased considerably (Al-Mailay, 2008). The antifertility activity of D. metel is shown in Fig. 7. However, in these studies, there was no specific identification of a compound that could be active as a contraceptive.

Metabolism of Datura metel seed compounds

We have found a study where authors used 0.15 mg/kg oral D. metel seeds aquas extract in rats to find out the metabolism of D. metel compounds. They have characterized 42 compounds from seed extract and studied thirteen bioactive compounds metabolic pathways. They found 61 compounds in blood plasma, 81 in urinary excretion, and 76 in stools. Though this might be the first study of full metabolic profiling of D. metel seeds, proper quantification is not mentioned (Xia et al., 2019).

Toxicological profile of Datura metel

More research on poisonous plants is crucial to avoid livestock losses (Panter et al., 2013). It is due to the fact that each plant contains thousands of compounds, and among them all, some may not be poisonous to us (Dutkiewicz et al., 2016). In fact, the toxic substances can be used for many purposes, such as herbicidal (Javaid et al., 2010), insecticidal, pesticidal, to kill cancer cells, and so on (Tariq et al., 2015; Shuping and Eloff, 2017). Datura is a toxic medicinal plant. All the parts of this herb are poisonous. It is because of the presence of poisonous tropane alkaloids and anticholinergic agents (e.g., atropine, hyosyamine, and scopolamine). Convulsions, acute confusion, dry mouth, fever, tachycardia, urine retention, hot-flushed dry skin, hallucinations, headache, dilated pupils, delirium, a weak and rapid pulse, coma, and even death are common signs and symptoms of Datura poisoning (Kam and Liew, 2002). The withametelins I, K, L, and N showed cytotoxicity activities against K562 (leukemia), BGC-823 (gastric), and A549 (lung) cancer cell lines, with IC_{50} values of 0.05 to 3.5 μM. Withamilin J depicted moderate cytotoxic activity against K562 and BGC-823 but less cytotoxicity against the A549 cell line (Pan et al., 2007). Other cytotoxic withametelins are J, M, O, P, 12-β-hydroxy-1,10-seco-withametelin B, and 1,10-seco-withametelin B.

Importantly, D. metel exhibited safety up to a 2000 mg/kg body weight dosage since it creates no observable sign of toxicity or death. Histological studies showed the minimized weight of the organs and necrotic modifications in the liver, followed by the increasing of ALP (serum alkaline phosphatase), SGOT (serum glutamic-oxaloacetic transaminase), and GPT (glutamyl pyruvic transaminase) (Bouzidi et al., 2011, Ogunmoyole et al., 2019).

Tropane alkaloids can be found throughout the plant, particularly in the leaf and seeds, and are poisonous. It includes atropine, hyoscyamine, and scopolamine. The central and peripheral muscarinic neurotransmission is inhibited by the tropane alkaloids, resulting in the anticholinergic syndrome (Schultes and Hofmann, 1979; Wijesekara and Iqbal, 2021; Kam and Liew, 2002); a possible mechanism is shown in Fig. 8.

Conclusion and future perspectives

D. metel possesses several phytochemicals with a wide range of pharmacological effects. Despite its toxicity, the plant holds significant promise as a potential source of plant-based therapeutics. Future research should focus on exploring the plant's therapeutic potential while ensuring proper safety precautions are taken. Advancements in

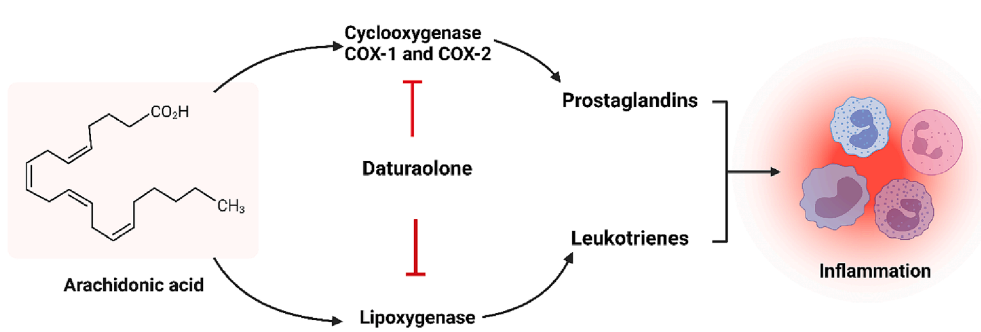

Fig. 7. Proposed anti-inflammatory and analgesic effect of daturaolone (Through COX-1 and COX-2 and lipoxygenase inhibition it may inhibits prostaglandins and leukotrienes production thus reduce in inflammation).

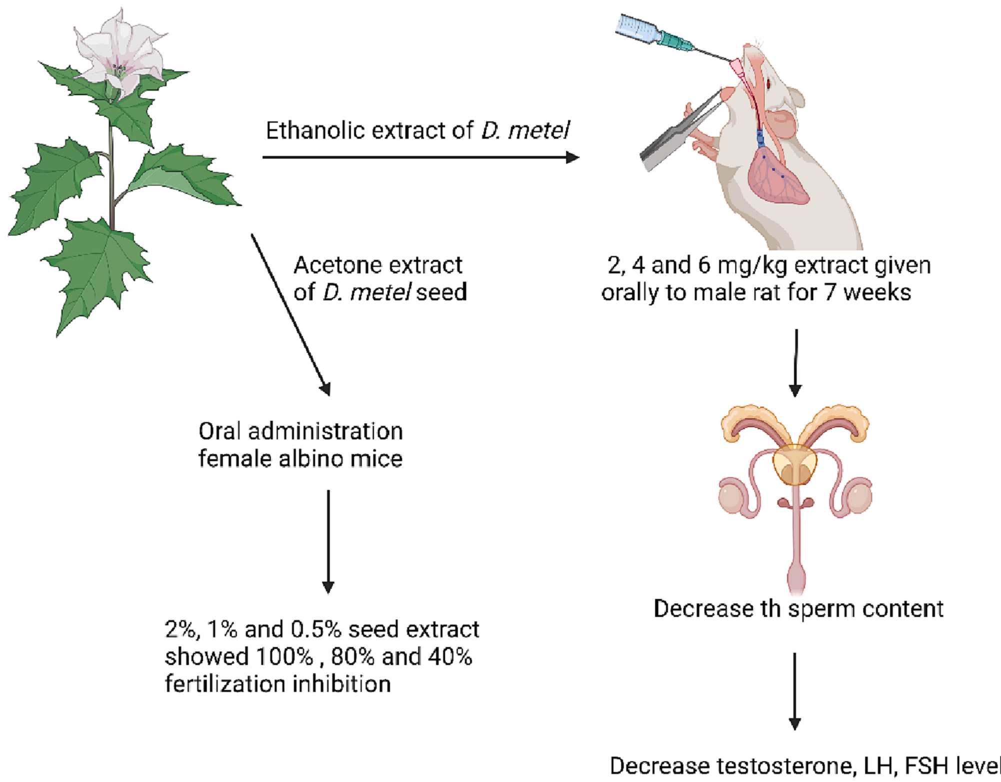

Fig. 8. Anti-fertility activity of *Datura metel* (Here, ethanolic extract of *D. metel* showed sperm content lowering activity this might be the result of bioactive compound of this plant decreasing testosterone, luteinizing hormone (LH) and follicle-stimulating hormone (FSH). On the other hand, acetone seed extract on female mice showed 100 percent antifertility action with 2% extract concentration).

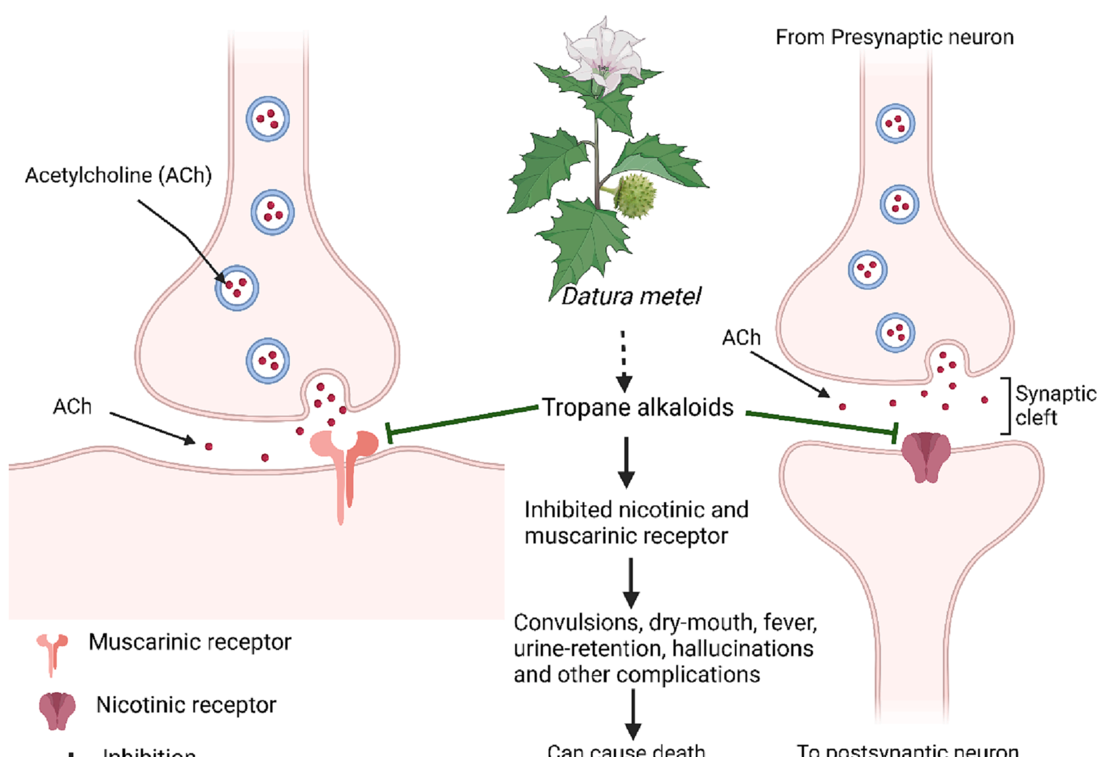

Fig. 9. Proposed toxicity mechanism of tropane alkaloids of *Datura metel* (Here, tropane alkaloids blockade the function of nicotinic and muscarinic receptors and neurotransmitter like acetylcholine (Ach) cannot bind with the targeted receptor which results anticholinergic syndrome).

technology and methodologies could lead to the discovery of novel compounds with beneficial biological activities that could help treat various diseases. *D. metel*, like many other medicinal plants, has the potential to contribute to the development of modern medicine and improve the quality of life for millions of people. Therefore, further exploration of the plant's pharmacological properties could lead to the development of new and effective drugs for the treatment of various ailments (Fig. 9).

A number of alkaloids found in the plant, such as atropine, scopolamine, and hyoscyamine, have been demonstrated to have anticholinergic, antispasmodic, and analgesic properties. D. metel is a viable option for the treatment of neurological conditions, including Alzheimer's and Parkinson's disease, because recent research has also indicated that it may have neuroprotective and anti-inflammatory qualities. Nonetheless, due to the plant's recognized toxicity and misuse potential, use for medical purposes must be done with caution. Future treatments and therapies will likely be more successful as a result of new insights into the possible advantages and hazards of D. metel that are anticipated to be revealed as research into the plant progresses.

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Data availability statement

Not applicable.

CRediT authorship contribution statement

Tawhida Islam: Conceptualization. **Iffat Ara:** Methodology. **Tariqul Islam:** Conceptualization. **Pankaj Kumar Sah:** Methodology. **Ray Silva de Almeida:** Software. **Edinardo Fagner Ferreira Matias:** Resources. **Cícero Lucas Gomes Ramalho:** Resources. **Henrique Douglas M. Coutinho:** Writing – original draft, Project administration. **Muhammad Torequl Islam:** Conceptualization, Supervision, Project administration.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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