Industrial Crops & Products 186 (2022) 115283

Contents lists available at ScienceDirect

Industrial Crops & Products

journal homepage: www.elsevier.com/locate/indcrop

Tropane alkaloids (hyoscyamine, scopolamine and atropine) from genus *Datura*: extractions, contents, syntheses and effects

Zhiwen Shi [a,b,c,1], Wenjin Zou [a,b,c,1], Zhiming Zhu [a,b,c], Ziwen Xiong [a,b,c], Shanying Li [a,b,c], Pan Dong [a,c,*], Zhenglin Zhu [a,**]

[a] School of Life Sciences, Chongqing University, Chongqing 401331, China
[b] Hongshen Honors School, Chongqing University, Chongqing 401331, China
[c] Key Laboratory of Plant Hormones and Development Regulation of Chongqing, Chongqing University, Chongqing 401331, China

ARTICLE INFO

Keywords:
Datura extract
Hyoscyamine
Scopolamine
Atropine
Synthesis
Function

ABSTRACT

Belonging to family Solanaceae, genus *Datura* is widely distributed all over the world and famous for its narcosis and acesodyne in ancient China. And *Datura* is also annoying due to the poisoning and hallucinogenic effects. Besides the medicine, it plays a magical role in seed germination and plant growth, and has good effects against plant diseases, insectsand weeding. Its main function components are tropane alkaloids (TAs), including hyoscyamine, scopolamine and atropine (HSA). They share a common tropane fragment (N-methyl-8-azabicyclo [3.2.1] octane). L-hyoscyamine and scopolamine are natural active ingredients in *Datura*, while atropine is an equal mixture of L-hyoscyamine and D-hyoscyamine, produced by the racemization of L-hyoscyamine during the extraction. As competitive antagonists of acetylcholine muscarinic (M-) choline receptors, HSA potently regulates the central nervous system (CNS). In addition, scopolamine shows effectiveness in the treatment of the respiratory and digestive system diseases, such as acute respiratory distress syndrome (ARDS) and gastrointestinal motility disorders. Hyoscyamine has remarkable effects on treating Parkinson's disease, bradyarrhythmias and genitourinary symptoms. Atropine is widely used in the treatment of myopia, amblyopia and organophosphorus poisoning. Recently, scopolamine-induced disease models play an important role in the exploration of the effects of drugs in amnesia, cognitive impairment and neuronal damage. In this review, we aim to summarize the contents of HSA in different *Datura* species and their influencing factors, performe an overview of the biosynthesis and chemical synthesis pathways and analyze the key synthetase in the NCBI database, highlight the effect of *Datura* extract and HSA on resisting plant insects and diseases, controlling weeds and treating different kinds of diseases in human.

1. Introduction

The genus *Datura*, Dicotyledonae, Angiosperm, is widely distributed in Asia, America, and North Africa. It usually grows in the wilderness and can also be used in landscape design. The main morphological features of *Datura* include: the erectness of flowers, oblique ascend/droop, long and trumpet-shaped corollas, ovate leaves; spiny surfaces of the capsule and oblate/nearly round seeds (Tsialtas et al., 2014; Sun et al., 2016). The classification of *Datura* has always been controversial. Until recent years, scholars suggest that the genus *Datura* contains 14 species indicated by the evidences from morphology, isoenzyme, and molecular biology (Jiao et al., 2002; Luna-Cavazos et al., 2008) (Table 1). Except for the semi-aquatic *D. ceratocaula* Ortega, other species are terrestrial annual herbs or perennial shrubs (Kariñho-Betancourt et al., 2015). The whole *Datura* plant is poisonous and there are numerous cases of human and animal poisoning after taking in the plant in large quantities by mistake all over the world (Kerchner and Farkas, 2020). The toxic symptoms include mydriasis, tachycardia, disorientation, delirium, hallucinations and restlessness (Ghorani-Azam et al., 2018). *Datura* is also used as poison in robbery, probably causing victims in coma or death of a heart disorder due to the severe anticholinergic syndrome (Le Garff et al., 2016). In addition, *Datura* has been abused in

* Corresponding author at: School of Life Sciences, Chongqing University, Chongqing 401331, China.
** Corresponding author.
E-mail addresses: dongpan@cqu.edu.cn (P. Dong), zhuzl@cqu.edu.cn (Z. Zhu).
[1] Both authors have equal contributions: Zhiwen Shi and Wenjin Zou

https://doi.org/10.1016/j.indcrop.2022.115283
Received 15 November 2021; Received in revised form 23 May 2022; Accepted 25 June 2022
Available online 5 July 2022
0926-6690/© 2022 Elsevier B.V. All rights reserved.

Table 1
The classification, origin and traditional uses of genus *Datura*.

Number	Species (Latin name)	Common Name	Origin	Traditional uses	References
1	*D. candida* (Pers.) Saff.	angle's trumpet, white angle trumpet, campana, borrachero, floripondio, anglabasun, campana de flor blanca, chanico sp.	Australia	earache	(Haegi, 1976;Benítez et al., 2018)
2	*D. ceratocaula* Ortega	torna-loca maddening plant	Central Mexico	N/A	(Beresford and Woolley, 1974; Kariñho-Betancourt et al., 2015)
3	*D. discolour* Bernh.	desert throne apple	Southern California, Arizona, New Mexico, Mexico, Northwestern Mexican Pacific coastal plains	asthma, toothache, hemorrhoid, wounds ulcer,otitis	(Bye and Sosa, 2013; Ibrahim et al., 2018; Barelay, 1959; Barclay; Kalemkiarian and Miller, 1957)
4	*D. ferox* L.	chamico	Argentina, Asia, America	asthma, pain, gout, boil, abscess, psychotropic drug, inflammation, hemorrhoid, anesthetic and antispasmodic drug	(Haegi, 1976;Benítez et al., 2018; Beresford and Woolley, 1974; Dupraz et al., 1994; Houmani et al., 1999; Ibrahim et al., 2018;Fu et al., 2011; Kariñho-Betancourt et al., 2015)
5	*D. quercifolia* Kunth	chinese thorn apple	Southwestern United States, Mexico, Algeria	lice, inflammation/massage, hemorrhoid	(Benítez et al., 2018; Ibrahim et al., 2018; Kariñho-Betancourt et al., 2015)
6	*D. kymatocarpa* Barclay	barclay *Datura*	Rio Balsas Valley, Mexico	N/A	(Ibrahim et al., 2018; Barclay)
7	*D. leichhardtii* F. Muell.	thorne apple, leichhardt's Datura, pituri	Australia, Western Australia and in Queensland	N/A	(Dhiman et al., 2012;Ibrahim et al., 2018; Alves and Evans, 1963)
8	*D. metel* L.	purple *Datura*, yangjinhua, garden Datura, horne of plenty, david bush, concombre zombie, cornicopio, devil's trumpet, angel trumpet, ummattai, kanaka	Asia	pain in the lung, cough, angina	(Benítez et al., 2018; Ibrahim et al., 2018)
9	*D. fastuosa* L.	N/A	Indonesia	antidiabetic activity, xanthine oxidase inhibitory activity, hypouricemic activity, spontaneous motor activity, barbituric sleeping, rectal temperature, apomorphine stereotypes, apomorphine hypothermia, catalepsy and ptosis induced by haloperidol, immobility induced by forced swimming, analgesic, scavenging free radical, antioxidant	(Ibrahim et al., 2018; Fu et al., 2011)
10	*D. innoxia* Mill.	prickly burr, angel trumpet, sacred *Datura*	North America, India, Mexico, South America, West Indies, North Africa	asthma, cough, inflammation, latido, stomachache, navel pain, rheumatism, muscle pains, strokes, diabetes, hemorrhoids, dengue, calentura, snakebite, hallucinogenic, neurotoxic pains, headache, peyote ceremony, lovesickness, diarrhea	(Alabri et al., 2014;Benítez et al., 2018; Huang et al., 2008; Shahwar et al., 2011; Dhiman et al., 2012;Ibrahim et al., 2018;Kariñho-Betancourt et al., 2015; Kam and Liew, 2002)
11	*D. velutinosa* V. R. Fuentes	N/A	Cuba	N/A	(Ibrahim et al., 2018)
12	*D. stramonium* L.	angel's tears, kala *Datura*, angel's trumpet, apple of Peru, black *Datura*, devil's apple, devil's trumpet, downy thorn apple, green dragon, hairy thorn apple, Hindu *Datura*, Indian apple, Jamestown weed, jimson weed, le reina de la noche, large-flowered throne apple, loco wood, mad apple, moon flower, oakleaf thorn apple, stink weed, stink wort, trumpet lily	Canada, Ontario, Quebec	cough, asthma, cold, catarrh, toothache, mumps, helminthiasis, hemorrhoids, rheumatism, joint pain, pimple, superficial tumor, ulcer, burn, erysipelas, parasite, inflammation, dermatological illness, pertussis, inflammation of the uterus, vaginal infection, menstrual blleding, jabor pain, headache, neuritis, neuralgia, tranquilizer - sedative central nervous system, gout, scare, trance, divination	(Benítez et al., 2018; Weaver and Warwick, 1984;Wei et al., 2011; Ibrahim et al., 2018)
13	*D. tatula* L.	N/A	Poland	radical scavenging activity	(Fu et al., 2011; Yamada et al., 2007)
14	*D. wrightii* Hort. ex Regel	sacred thorn apple, toloach	Western Texas, California, Mexico	snake bite, asthma, pain, fracture, swelling, rheumatism, arthritis	(Haegi, 1976;Benítez et al., 2018; van Dam et al., 1999;Ibrahim et al., 2018; Ness and Bressmer, 2005)
15	*D. arenicola* Gentry ex Bye & Luna	chamica	Mexico	N/A	(Robert et al., 1991)
16	*D. lanosa* A.S. Barclay ex Bye	N/A	Mexico	asthma, headache, skin ulcers, sore, bruise, swelling, boil, drunkenness, peyote ceremony, vision inductor	(Benítez et al., 2018)
17	*D. meteloides* Dunal	N/A	N/A	pimples, rice blast, ulcer, muscle pain, hemorrhoid, otitis	(Benítez et al., 2018)

the folk for its intoxicating and hallucinogenic effects (Silvia et al., 2017). Despite a variety of drawbacks, *Datura* plants are world-famous for the excellent therapeutic effects on human diseases, such as asthma and stomach cramps and their useage as an anesthetic since ancient times (Deng et al., 2011). Many famous drugs have ingredients from *Datura* plants, including the Chinese traditional narcotics Mafeisan and Yangjinhua capsules for psoriasis (Wang, 2014). In recent years, the possibility of the application of *Datura* extract in agriculture has been studied extensively, such as the interference of plant growth and the prevention of plant diseases/insects. (Zheng and Li, 2008).

The history of applications and researches of *Datura* extract and HSA can go back to the origins of Hinduism and Buddhism (Geeta and Gharaibeh, 2007) (Fig. 1). In recent years, scientists have conducted comprehensive and in-depth researches on the applications of *Datura* extractions, HSA contents and biological/chemical synthesises synthesises and effects in medicine, agriculture and other fields. In the following parts, the contents of HSA in different *Datura* species and their influence factors are summarized in detail. The extraction method, biosynthesis and chemical synthesis pathways are described in a sorted order. These highlight the effects of *Datura* extract and HSA on human beings, animals, plants and microorganisms for providine references for application.

2. Extraction methods

Datura extract usually refers to the aggregate of substances obtained through extraction by water or organic matter. With the technology development, the extraction methods have become plentiful (Table 3). Direct leaching with fresh tissues at room temperature and dry powder immersion with boiling or normal water are the most common methods of water extraction. Organic solvents include methanol, ethanol, methyl sulfoxide, petroleum ether, ethyl acetate, acetone, etc. Methanol and ethanol are the most commonly used. In order to have a comprehensive extraction, the solvents usually contain multiple organic reagents, such as the combination of methanol, ethanol and acetone (Sun et al., 2012) and the combination of ethanol and chloroform, etc. (Kagale et al., 2004). The specific extraction methods use organic solvents including soaking centrifugal extraction, immersion ultrasonic extraction, solicitation, etc.(Table 3). Different solvents or combinations of solvents usually lead to different results. In soaking centrifugal extraction, ethanol extraction has a better effect on killing nematodes than water extraction (Babaali et al., 2017). In immersion ultrasonic extraction, ethyl acetate extraction is the best, followed by methanol extraction (Zhou et al., 2009). While using the cold dipping method, the crude methanol extract has the best effect in killing armyworm in 5 solvents (Zhou et al., 2008). In general, compared with water extraction, there are multiple organic solvent extraction methods and these methods have a wide application.

3. Content

The levels of HSA have been detected in many species of *Datura*, such as *D. stramonium* L., *D. quercifolia* Kunth, *D. ferox* L., *D. discolour* Bernh., etc. (Table 4). The contents of HSA are highly variable in different species of *Datura*, for example, *D. stramonium* plants treated with acetylsalicylic acid has the highest TTAs (total tropane alkaloids) content (11580 μg/g) (Robert et al., 1991), followed by *D. lanosa* vegetative parts (6900 μg/g) (Kariñho-Betancourt et al., 2015), while the juvenil stage (JS) leaves of *D. ferox* and *D. discolour* are the lowest (4 μg/g) (Parr et al., 1990). Remarkable differences in the hyoscyamine level between species are still observed, ranging from 0.56 μg/g (*D. kymatocarpa*) (Parr et al., 1990) to 8100 μg/g (*D. stramonium*) (Hilton and Rhodes, 1990). The highest scopolamine level is observed in *D. reburra* (6980 μg/g) (Hiraoka et al., 1996), while the lowest level is detected in *D. metel* (9 μg/g) (Bejeuhr, 1995; Parr et al., 1990). Atropine has relatively few studies and the species difference also exists, such as *D. innoxia* (5.7 μg/g) (Boros et al., 2010) and *D. metel* (1329 μg/g) (Shakeran et al., 2015). For the same species, the accumulation of HSA in different organs of *Datura* is also significantly different, for example, in the root, stem, flower and seed of D. Ceratocaula, the hyoscyamine content is 160 μg/g, 420 μg/g, 410 μg/g and 250 μg/g, respectively (Berkov et al., 2006). For the same organ, the content of HSA during its growth period is changeable. Taking the leaves of *D.reburra* as an example, the levels of TTAs, hyoscyamine, scopolamine and atropine in JS are 220 μg/g, 2.86 μg/g, 197.47 μg/g, respectively, but those in the reproductive stage (RS) are 580 μg/g, 19.1 μg/g, 499.47 μg/g, respectively. If D. stramonium is treated with poultry manure, vermicompost or nitrogen fertilizer nutrient systems, the contents of atropine and scopolamine are different. Vermicompost results in the highest content (24.83 μg/g and 29.77 μg/g), while nitrogen fertilizer results in the lowest (13.08 μg/g and 18.13 μg/g), suggesting the type of nutrient supply affects HSA contents (Hiraoka et al., 1996; Kariñho-Betancourt et al., 2015).

Some new technologies or methods are applied to improve the HSA content in *Datura* plants. Plant tissue culture techniques, especially the hairy root culture techniques, are used to increase TAs levels in D. stramonium, D. quercifolia, D. ferox etc. The hyoscyamine content of hairy roots of D. stramonium reached 8100 μg/g, which is the highest value for hyoscyamine detected to date (Parr et al., 1990; Payne et al., 1987). The content of HSA could be increased by induction treatment with nanoparticles. Treated by nano silver in *D. metel*'s hairy roots, the content of atropine reached 1329 μg/g, a increase of 11.7% comparied with the control (Shakeran et al., 2015). Similar results were obtained in *Hyoscyamus reticulatus* L., induced by iron oxide nanoparticles (Moharrami et al., 2017). Under the synergistic effect of elicitor acetylsalicylic acid, the content of TTAs in *D. stramonium* is 42% higher than that of the control group, reaching 11580 μg/g (Harfi et al., 2018). When the content of TTAs in diploid *D. stramonium* is 2730 μg/g, while tetraploid plants contain 5160 μg/g, suggesting the polyploid breeding method can significantly increase the HSA content (Rowson, 1944). In addition, scientists also applied biotechnology to change the contents of HSA in some specices of solanaceae family. In *Atropa Belladonna* L., the knock out of the gene PYRROLIDINE KETIDE SYNTHASE and the overexpression of the genes Putrescine N-methyltransferase (*PMT*) and hyoscyamine 6β-hydroxylase (*H6H*) can reduce and increase the HSA accumulation in tissues, respectively (Xia et al., 2016; Hasebe et al., 2021). Recent study has shown that by overexpressing the calmodulin

Note: 1. *D. ferox* and *D. quercifolia* showed morphological similarity by the method of numerical taxonomy (Fu et al., 2011). 2. According to the Species 2000 database and the United States Department of Agriculture, *D. fastuosa*, *D. metel*, and *D. innoxia* were confirmed as the same species (Fu et al., 2011). 3. It is recorded in the Flora of China that *D. stramonium* and *D. tatula* are synonyms, which is also confirmed by ITS sequence analysis (Wei et al., 2011). Secondary metabolites tropane alkaloids (TAs) refer to a class of compounds with 8-nitrogen heterocyclic octane mother nucleus, including flavonoid, sesquiterpenoids, alcohols, diols, triols and alkaloids. (Jia et al., 2018). Most TAs are the oldest drugs derived from poisonous Solanaceae plants, including *Atropa*, *Brugmansia*, *Datura*, *Duboisia*, *Hyoscyamus*, *Scopolia*, etc. (Griffin and Lin, 2000; Holzman, 1996). Genus *Datura* is thought to contain a large amount of TAs, including hyoscyamine ($C_{17}H_{23}NO_3$) and scopolamine ($C_{17}H_{21}NO_4$). Hyoscyamine is unstable during extraction and can be racemic into atropine ($C_{17}H_{23}NO_3$). (Ibrahim et al., 2018). All parts of *Datura* plants contain these alkaloids, which become a good resource plant to extract HSA (Tsialtas et al., 2018). HSA share a common tropane fragment (N-methyl-8-azabicyclo[3.2.1] octane) (Vitale et al., 1995; Wang et al., 2010; Chen et al., 2017; Ullrich et al., 2017), while their physiochemical properties are different (Table 2). HSA are M-choline receptor blockers and are effective in modulating the central nervous system (CNS). In addition, they have significant efficacy in other diseases, such as hyoscyamine for treating Parkinson's disease, bradyarrhythmias, etc. (Srimathi et al., 2018); scopolamine for respiratory diseases, digestive diseases, etc. (Wigenstam et al., 2021); and atropine for eye diseases and organophosphorus poisoning relief (García Del Valle and Alvarez-Lorenzo, 2021).

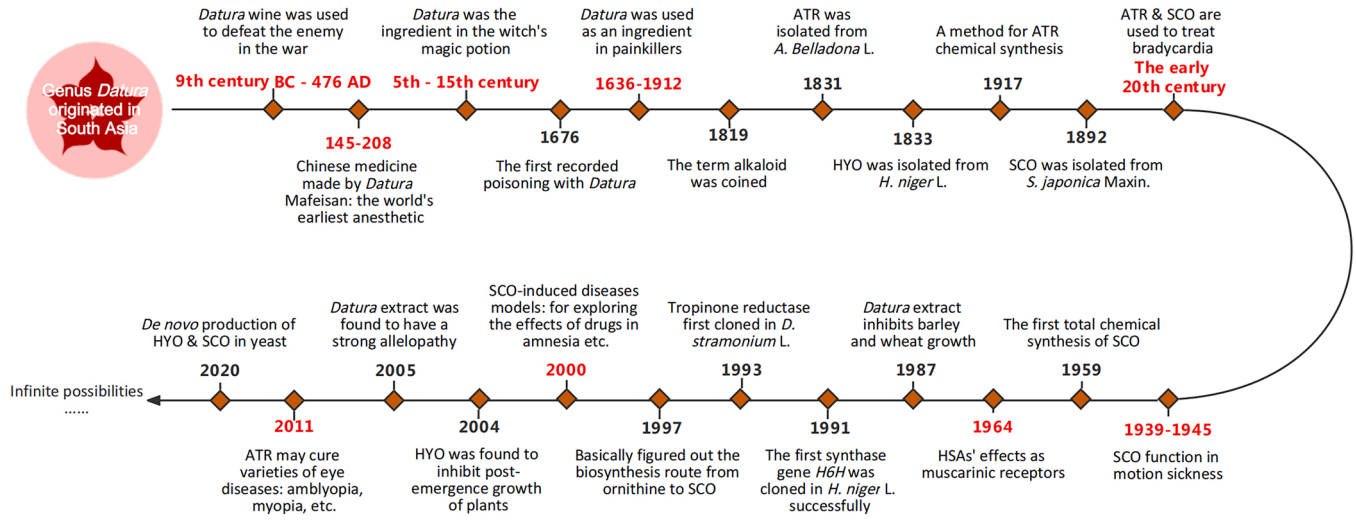
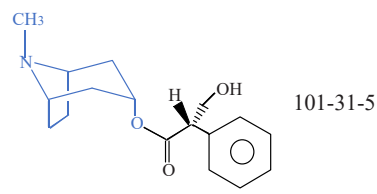
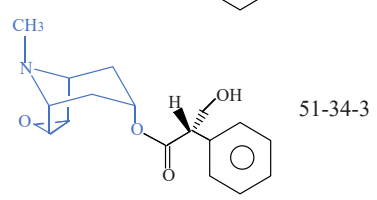
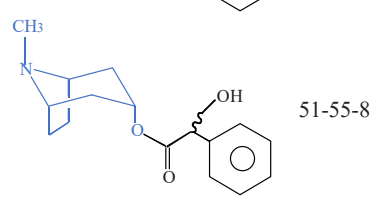


Fig. 1. The important events in the history of applications and researches of *Datura* extract and HSA. Note: The years in black color denote that the incident happened exactly that year, while the years in read color denote that the events were uncertain but there were substantial research or applications near that year. ATR, atropine. HYO, hyoscyamine. SCO, scopolamine. HSA. hyoscyamine, scopolamine and atropine. The *Datura* flower icon is from https://www.iconfont.cn.

Table 2
Structure and physicochemical properties of HSA* (Vitale et al., 1995; Wang et al., 2010).

Name	Molecular formula	physicochemical property	IUPAC Name * *	Chemical structure	CAS # * **
Hyoscyamine	$C_{17}H_{23}NO_3$	White needle crystal, soluble in dilute acid, chloroform, ethanol and other organic solvents, insoluble in ether or cold water.	(8-Methyl-8-azabicyclo [3.2.1]octan-3-yl) (2 S)− 3-hydroxy-2-phenyl-propanoate		101–31–5
Scopolamine	$C_{17}H_{21}NO_4$	White crystalline powder, odorless, bitter, alkaline in aqueous solution, soluble in ethanol and dilute acid, soluble in chloroform (1:1), soluble in water (1:280), ether (1:69), benzene (1:159)	9-Methyl-3-oxa-9-azatricyclo [3.3.1.02,4]nonan-7-ol (-)-alpha-(hydroxymethyl) benzeneacetate		51–34–3
Atropine	$C_{17}H_{23}NO_3$	White or colorless crystal, soluble in chloroform and ethanol, but insoluble in ether, petroleum ether and water	(8-Methyl-8-oxido-8-azoniabicyclo[3.2.1]octan-3-yl) 3-hydroxy-2-phenyl-propanoate		51–55–8

Note: * HSA: Hyoscyamine, scopolamine and atropine; * * CAS #: Chemical Abstracts Service Number; * ** IUPAC Name: International Union of Pure and Applied Chemistry Name; Blue part in chemical structure: tropane fragment (N-methyl-8-azabicyclo[3.2.1] octane)

gene *AbCaM1* in the lateral roots of *Atropa Belladonna* L., the content of hyoscyamine and scopolamine in the leaves can be increased by 4.01 and 4.11 times, respectively, indicating that increased Ca^{2+} concentration can promote the biosynthesis of HSA (Zhang et al., 2022). The concentration of HSA in *Hyoscyamus niger* L. is improved by EMS based mutagenesis (Ajungla et al., 2009). The above information suggests the transgenic transformation of the key synthetic enzyme genes in *Datura* might be a promising method to improve the levels of HSA.

4. Synthesis

Due to the sharing of a common tropane fragment, their are some common synthetic steps in the plant. Hyoscyamine can be firstly generated, and further atalyzed into scopolamine with the hyoscyamine 6β-hydroxylase (H6H). Atropine is obtained by the racemic of hyoscyamine. Nevertheless, the HSA content in plants is very low, and it is difficult (or expensive) to independently separate them from the extract, so biosynthesis is far from meeting the medical and clinical needs (Wang et al., 2011), and the exploration of chemical synthesis is on the rise. The relationship between chemical synthesis and biosynthesis is nearly synergistic. Robinson's chemical synthesis of tropinone inspires the first biosynthetic theory of HSA in plants. Accordingly, the biosynthetic reactions in plants have stimulated new perspectives on the chemical synthesis of HSA.

4.1. Biosynthesis pathways of HSA

Plants are the main sources of HSA which are synthesized in the roots

Table 3
Datura Extraction Methods.

Extraction Methods	Solvents	Key Steps	References
Boiling water leaching*	Distilled water	Extract twice with boiling water and concentrate by evaporation.	(Ruijia et al., 2010)
Dry powder water immersion*	Distilled water	Configure different concentration solutions by different weight dry powders.	(Cai et al., 2012)
Direct leaching*	Distilled water	Cut fresh leaves and soak at room temperature.	(Cheng et al., 2011)
Soaking centrifugal extraction	Distilled water, ethanol, methyl sulfoxide	Shake and soak the dry powder, filter under pressure, centrifuge the filtrate, concentrate by evaporation and dilute with solvent.	(Babaali et al., 2017)
Immersion ultrasonic extraction* *	Petroleum ether, ethyl acetate, methanol	Soak by solvent, extract by ultrasonic, concentrate under reduced pressure and dilute by acetone.	(Zhou et al., 2009)
Ethanol extraction* *	Ethanol	Extract samples 3 times and concentrate under reduced pressure.	(Zhu et al., 2015)
Solicitation* *	Ethanol	Extract the dry powder with Soxhlet extractor, reflux ethanol and filters.	(Xiufen and Guangwen, 2001)
Total alkali extraction* *	Ethanol, chloroform	Extract with acidic ethanol, acidify, filter, alkalize and extract by chloroform.	(Lu et al., 2006)
Methanol extraction* *	Methanol, ethanol, acetone	Extract plant powder with ethanol, leach ultrasonically, concentrate under reduced pressure and dissolve in methanol or acetone ultrasonically.	(Sun et al., 2012)
Cold dipping* *	The organic solvent (such as methanol, ethanol, propanol, petroleum ether, ethyl acetate)	Crush samples, soak 3 times and distill under reduced pressure.	(Zhou et al., 2008)
Petroleum ether extraction* *	Petroleum ether	Dry the sample, crush and extract, and concentrate under reduced pressure.	(Bachheti et al., 2018)

Note: The symbol "* " represents the water extraction methods, "* *" represents the organic extraction methods, and others are organic and water mixed extraction methods

and then transported into the xylem (Payne et al., 1987; Schlesinger et al., 2021). Since the structure of the tropane ring system was first elucidated in 1901, scientists spent more than 100 years to find out the synthetic paths of HSA in solanaceae plants (Humphrey and O'hagan, 2001) (Fig. 2). Putrescine is the common precursor of HSA synthesis and there are two methods for getting putrescine in plants: (1) directly obtaining by decarboxylation of ornithine through ornithine decarboxylase (ODC); (2) using arginine as the precursor and finally forming through 3 continuous steps with 3 key enzymes arginine decarboxylase Decarboxylase (ADC), agmatine iminohydrolase (AIH), and N-carbamoylputrescine amidohydrolase (CPA). In the synthesis of HSA in *Datura* plants, the arginine pathway is mainly involved (Zhang et al., 2004). Putrescine N-methyltransferase (PMT) catalyzes the methylation of putrescine to N-methylputrescine (Robins et al., 1991; Li et al., 2014; Long et al., 2013), which is further oxidized to generate 4-aminobutanal by N-methylputrescine oxidase (MPO) (Qiu, 2019; Yan et al., 2014). The spontaneous cyclization of 4-aminobutanal forms N-methyl--Δ^1-pyrrolinium cation, which is followed by the generation of tropinone through a series of dehydrogenation with pyrrolidine ketide synthase (PYKS) and tropinone synthase (CYP82M3) (Huang et al., 2019). Tropinone is further reduced to tropine and pseudotropine by tropinone reductase (TR) I and II, respectively. Tropine and pseudotropine cannot transform into each other in plants (Fu, 2020). Pseudotropine can futher generate calystegin and other esters, while tropine is a synthetic precursor of hyoscyamine, atropine and scopolamine (Kim et al., 2016; Dräger, 2006). Torpine and phenyllactic acid are condensed to littorine through esterification with the littorine synthase (LS) and phenyllactate UDP-glycosyltransferase (UGT1) (Qiu et al., 2020). Phenyllactic acid can be obtained from phenylalanine through the catalysis of aromatic amino acid aminotransferase (ArAT4) and phenylpyruvic acid reductase (PPAR) (Qiu et al., 2018). *ArAT4* was firstly cloned and identified in *Atropa belladonna* in 2014 (Li et al., 2017; Bedewitz et al., 2014). The mechanism of later synthesis reaction from littorine has been controversial for more than 10 years. One theory is that a vitamin-B12-like isomerase is involved[47] (Shakeran et al., 2015), and the other hypothesis proposes that there is a oxidation product intermediate hyoscyamine aldehyde, which can be further reduced to hyoscyamine by hyoscyamine dehydrogenase (HDH) (Nguyen et al., 2015; Qiu et al., 2021). In 2006, Covell et al. cloned *CYP80F1* (littorine mutase/ monooxygenase), which is involved in the production of hyoscyamine aldehyde, strongly supporting the second hypothesis (Li et al., 2006). In the final stage of scopolamine biosynthesis, H6H catalyzes the hydroxylation of hyoscyamine and the subsequent epoxidation to produce scopolamine (Qiang et al., 2015; Li et al., 2013). *H6H* is the first HSA synthesis pathway gene to be cloned in *Hyoscyamus niger* in 1991, and then it is found in more and more plants, including D. stramonium and *D. metel* (Xia et al., 2016).

The above key synthetase gene sequences in genus *Datura* were retrived from NCBI database and sorted in Table 5, which provide the detailed information about species, GenBank number, lengths, coding sequences, number of amino acid residues, etc. Except for those genes, the rest synthetase genes have not been studied much in genus *Datura* and need for further exploration. With the booming development of synthetic biology, *de novo* synthesis of HSA in microorganisms has been carried out. The *de novo* HSA biosynthesis pathway was started in 2019, when Ping et al. achieved the *de novo* production of N-methyl-pyrrolinium in *E. coli* and *S. cerevisiae* (Huang et al., 2021). Later, the production of tropine and pseudotropine were achieved in yeast at the same year (Ping et al., 2019). The significant milestone breakthrough came in 2020, when Srinivasan and Smolke successfully produced hyoscyamine and scopolamine in a yeast from simple amino acids and sugars by integrating approximately twenty enzymes (Srinivasan and Smolke, 2020).

4.2. Chemical synthesis pathways of HSA

Scopolamine is an optically and biologically active L-optically isomer, which is fairly stable after racemization (Kohnen-Johannsen and Kayser, 2019). Likewise, the pure hyoscyamine is a left optical isomer which is unstable, and rapidly racemized to form stable atropine. Therefore, the main products of chemical synthesis are scopolamine and atropine.

In 1955, Fodor et al. made the first successful synthesis of scopolamine by chemical method (Fodor et al., 1956). After subsequent improvements to make each step suitable for the requirements of industrial production, the synthesis protocol is determined and 8 consecutive steps are ascertained (Fig. 3A) (Institute and Factory, 1977). The process starts with the reduction of 6β-hydroxy tropinone to 3α, 6β-dihydroxy tropinone, which is followed by the formation of 3α, 6β-diacetoxy tropane through diacetylation. And then 3α, 6β-diacetoxy tropane is selectively hydrolyzed to 3α-acetoxy-6β-hydroxy tropan, which further

Table 4
Contents of TAs from different organs of *Datura* species.

Species	Organ	TTAs[a]	Hyoscyamine	Scopolamine	Atropine	References
A. *stramonium* L.	JS[b] Leaves	410	0.84	161	/	(Kariñho-Betancourt et al., 2015)
	RS[c] Leaves	1400	5.30	634	/	(Kariñho-Betancourt et al., 2015)
	Root culture organ	1800–2200	1053	0	/	(Parr et al., 1990)
	Flowers	/	7.29 or 8.33	/	/	(Berkov and Pavlov, 2004)
	Seeds	/	320–8100	/	/	(Hilton and Rhodes, 1990)
	Leaves and seeds	6100	/	/	/	(Kariñho-Betancourt et al., 2015)
	Roots	/	/	856.2	/	(Lei, 2011)
	Stems	/	94	92	/	(Zhang et al., 2015)
	Leaves	6600	/	/	/	(Kariñho-Betancourt et al., 2015)
	Seed coats	/	/	753	/	(Lei, 2011)
	Callus	/	/	231.1	/	(Hergenisa, 2012)
	JS stems	/	240	/	/	(Zhao, 2011)
	Peel	2310	/	/	/	(Cui, 2009)
	Medicinal wine soaked in fruit	/	/	427.9–433.5	/	(Kadir, 2017)
	Fruit in medicinal wine	/	116	79	/	(Zhang et al., 2015)
	Whole plants	/	0.36–0.69	1.69–2.71	/	(Friedman and Levin, 1989)
	Leaves(Diploid)	/	/	39–84	/	(Xue et al., 2011)
	Leaves(Tetraploid)	100–600	/	/	/	(Kariñho-Betancourt et al., 2015)
	Leaves (irrigation regimes AWC[d]	1620	/	/	/	(Cui, 2009)
	55%)	/	/	22.73	/	(Lei, 2011)
	Leaves (irrigation regimes AWC	/	108	113	/	(Zhang et al., 2015)
	35%)	1030	/	/	/	(Cui, 2009)
	Leaves (irrigation regimes AWC	/	96	57	/	(Zhang et al., 2015)
	15%)	3170–4730	/	/	/	(Shang, 2016)
	Leaves (poultry manure nutrition)	/	/	14.11	/	(Lei, 2011)
	Leaves (vermicompost nutrition)	/	70	/	/	(Zhao, 2011)
	Leaves (nitrogen fertilizer nutrition)	2530	/	/	/	(Cui, 2009)
	Plants treated with acetylsalicylic	/	4.32, 6.15	6.64, 6.25	/	(Berkov and Pavlov, 2004)
	acid	2500	/	/	/	(Zhang and Tang, 1958)
		/	/	432.7	/	(Lei, 2011)
		/	100	51	/	(Zhang et al., 2015)
		/	200	/	/	(Zhao, 2011)
		290	/	/	/	(Cui, 2009)
		2688	/	1084	/	(An, 2012)
		132	11.6	12.3	/	(Li, Wang et al., 2012)
		/	87.6	526	/	(Zhang et al., 2015)
		2385	99	93.2	/	(Zhang et al., 2015)
		1102	216	75	/	(Li, Wang et al., 2012)
		/	63.3	495	/	(Lei, 2011)
		/	/	89.4	/	(Zhang et al., 2021)
		/	650	18.89	/	(Zhang et al., 2021)
		3730–3850	300	/	/	(Xu and Zhou, 1965)
		2730	2047.5	400.5	290.9	(Rowson, 1944)
		5160	4041.8	670.8	447.4	(Rowson, 1944)
		/	/	8.23	12.52	(Alinejad et al., 2020)
		/	/	16.29	19.59	(Alinejad et al., 2020)
		/	/	45.04	29.14	(Alinejad et al., 2020)
		/	/	21.66	23.33	(Alinejad et al., 2020)
		/	/	29.77	24.83	(Alinejad et al., 2020)
		/	/	18.13	13.08	(Alinejad et al., 2020)
		11580	/	/	/	(Harfi et al., 2018)
D. quercifolia Kunth	JS leaves	38	0.7	30.89	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	100	11.14	71.42	/	(Kariñho-Betancourt et al., 2015)
	Root culture organ	420	419	Traces	/	(Parr et al., 1990)
D. ferox L.	JS leaves	20	17.83	164.59	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	120	125	1014.8	/	(Kariñho-Betancourt et al., 2015)
	Root culture organ	4–85	849	43	/	(Parr et al., 1990)
	Seeds	/	/	1200–3400	/	(Delayno, 1994)
D. discolour Bernh.	JS leaves	20	1.13	183.76	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	120	13.58	1758	/	(Kariñho-Betancourt et al., 2015)
D. innoxia Mill.	Root culture organ	10–490	486	110	/	(Parr et al., 1990)
	Seeds	3000	2100	900	/	(Chen et al., 2019)
	Whole plant	728.16	/	/	/	(Zheng, 1980)
	Leaves	2530	/	/	/	(Zhang and Tang, 1958)
	Corolla	/	/	1350	/	(Lu and Li, 1979)
	nectar	/	/	157, 20	5.70	(Boros et al., 2010)
D. kymatocarpa Barclay	JS leaves	490	0.56	246.02	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	3500	3.22	2490	/	(Kariñho-Betancourt et al., 2015)
D. Pruinosa Greenm.	JS leaves	170	1.83	59.05	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	280	5.88	85.25	/	(Kariñho-Betancourt et al., 2015)
D. reburra Barclay	JS leaves	220	2.86	197.47	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	580	19.1	499.47	/	(Kariñho-Betancourt et al., 2015)
	Seeds	/	/	2940	/	(Hiraoka et al., 1996)

(*continued on next page*)

Table 4 (*continued*)

Species	Organ	TTAs[a]	Hyoscyamine	Scopolamine	Atropine	References
	Flowers	/	/	6980	/	(Hiraoka et al., 1996)
	Leaves	/	/	420	/	(Hiraoka et al., 1996)
D. wrightii Hort. ex Regel	JS leaves	130	32.43	99	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	1910	427.15	1130	/	(Kariñho-Betancourt et al., 2015)
	Root culture organ	20–800	820	15	/	(Parr et al., 1990)
D. lanosa A.S. Barclay ex Bye	Vegetative parts	4100–6900	/	/	/	(Bye and Sosa, 2013)
	Leaves	/	3900	4100	/	(Bye and Sosa, 2013)
	Stems	/	2500	2600	/	(Bye and Sosa, 2013)
	Immature fruits	/	2200	2300	/	(Bye and Sosa, 2013)
	Roots	/	3900	4100	/	(Bye and Sosa, 2013)
	JS leaves	300	8.67	291.58	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	1730	13.81	1607	/	(Kariñho-Betancourt et al., 2015)
D. metel L.	JS leaves	300	0.98	186.08	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	2970	37.41	2562	/	(Kariñho-Betancourt et al., 2015)
	Root culture organ	1000–2000	561	9	/	(Bejeuhr, 1995; Parr et al., 1990)
	Fruits	1200	/	/	/	(Bejeuhr, 1995)
	Seeds	2000–5000	/	/	/	(Bejeuhr, 1995)
	Flowers	/	/	1900	/	(Qiao et al., 1994)
	Leaves	/	/	1900	/	(Hiraoka et al., 1996)
	Whole plant	/	/	2330	/	(Yu et al., 1992)
	Processed Chinese medicine	/	/	3260	/	(He et al., 1999)
	Raw product of Chinese medicine	/	/	6600	/	(Qiao et al., 1994)
	Corolla	3030	/	2550	/	(Zhang and Tang, 1958; Hiraoka et al.,
	Nectar	/	/	3500	/	1996)
	Hairy root treated with $AgNO_3$	940.54	/	135.5	/	(Qiao et al., 1994)
	Hairy root treated with nanosilver	/	/	208.3	/	(Zheng, 1980)
	Inflorescence	/	/	3098	/	(Shu and Li, 2015)
	Roots	/	/	2770	/	(Shu and Li, 2015)
		/	/	128.22	4.11	(Lu and Li, 1979)
		/	/	/	420	(Boros et al., 2010)
		/	/	/	1329	(Shakeran et al., 2015)
		/	/	850	Nd	(Shakeran et al., 2015)
		/	/	780	Nd	(Naqvi et al., 1998)
						(Naqvi et al., 1998)
D. ceratocaula Ortega	JS leaves	220	0.76	187.61	/	(Kariñho-Betancourt et al., 2015)
	RS leaves	450	1.58	219.05	/	(Kariñho-Betancourt et al., 2015)
	Roots	/	160	70	/	(Berkov et al., 2006)
	Stems	/	420	200	/	(Berkov et al., 2006)
	Flowers	/	410	340	/	(Berkov et al., 2006)
	Seeds	/	250	70	/	(Berkov et al., 2006)
D. fastuosa L.	Seeds	/	/	6310	/	(Hiraoka et al., 1996)
	Whole plant	576.46–829.50	/	/	/	(Zheng, 1980)

Note: **a** TTAs: Total tropane alkaloids; per unit: μg/g; **b** JS: Juvenil stage; **c** RS: Reproductive stage; **d** AWC: Available water content in the soil.

reacts with p-toluenesulfonyl chloride to form 3α-acetoxy-6β-p-toluenesulfonyl oxytropane. Thereafter, 3α-acetoxy-6β-p-toluenesulfonyl oxytropane is eliminated by base catalysis to get 3α-acetoxy-tropane-6, which is further hydrolyzed to obtain tropine 6-ene-3α-alcohol hydrochloride after removing the acetyl group. Tropine 6-ene-3α-alcohol hydrochloride is esterified with acetyltropinyl chloride and hydrolyzed to 6, 7-racemic dehydroatropine, which is further epoxized to obtain racemic scopolamine. At last, scopolamine is produced by the combined action of acemic scopolamine and hydrobromic acid (Afewerki et al., 2019). In other synthetic attempts, scopolamine was synthesized by using 6,7-dehydrotropine as a key intermediate. Rhodium-catalyzed [4 + 3] cycloaddition chemistry and a modified Robinson-Schopf reaction were each independently evaluated for their utility in constructing this key intermediate. Both synthetic approaches gave comparable overall yields (Nocquet and Opatz, 2016; Harmata, 2010). However, at this stage, the chemical synthesis of scopolamine is still expensive and less efficient than the extraction from plants (Lakstygal et al., 2019). More researches on chemical synthesis are required for cost reduction.

The first attempt to build the chemical structure of atropine was in 1863 (Kraut, 1863). The full chemical synthesis of atropine was reported by Willstätter in 1901 as a process that starts from cycloheptanone which undergoes a 8-step conversion into cycloheptatriene (Willstätter, 1901) (Fig. 3B). Sequential bromination of cycloheptatriene replaces bromine with dimethylamine and reduces one of the two double links, resulting in 1-dimethylaminocyclohept-4-en finally. Followed by bromination of the remaining double link, a ring is created in 2-bromotropane salt that produces tropidine upon reaction with bases. Subsequent reduction of tropidine generates tropine, whose fusion with tropic acid in thepresence of hydrogen chloride produces atropine. In 1917, Robinson proposed a new and efficient method to synthesize atropine based on the condensation of three components, including succinaldehyde, methylamine and acetonedicarboxylic acid, with an impressive yield of 42% in the laboratory (Li et al., 2017; Robinson, 1917) (Fig. 3B). Although the synthesis of atropine is complex, the synthesis method is essential in the built of the chemical structure and the guidance to related researches in biosynthesis (Fu, 2020). Chemical synthesis of atropine is much more efficient than plant extraction and could be applied in large-scale industrial production. Recent research reported nonlinear optimisation of different separation design options for atropine continuous pharmaceutical manufacturing (CPM) to pursue cost minimisation. CPM can revolutionize industrial efficiency via potential operational and economic benefits without expensive and time-consuming experimental campaigns. However, systematicly comparative evaluation of alternative processes for operational feasibility and economic viability for atropine CPM is needed to be conducted (Diab et al., 2019; Bedard et al., 2017). It may also inspires the built of the protocols of scopolamine production by combining chemical synthesis and biosynthesis based on the efficent catalyses of H6H in near future.

From the mid-1900' s till now, the methods for key tropane intermediates in chemical synthesis of HSA (such as tropinone and

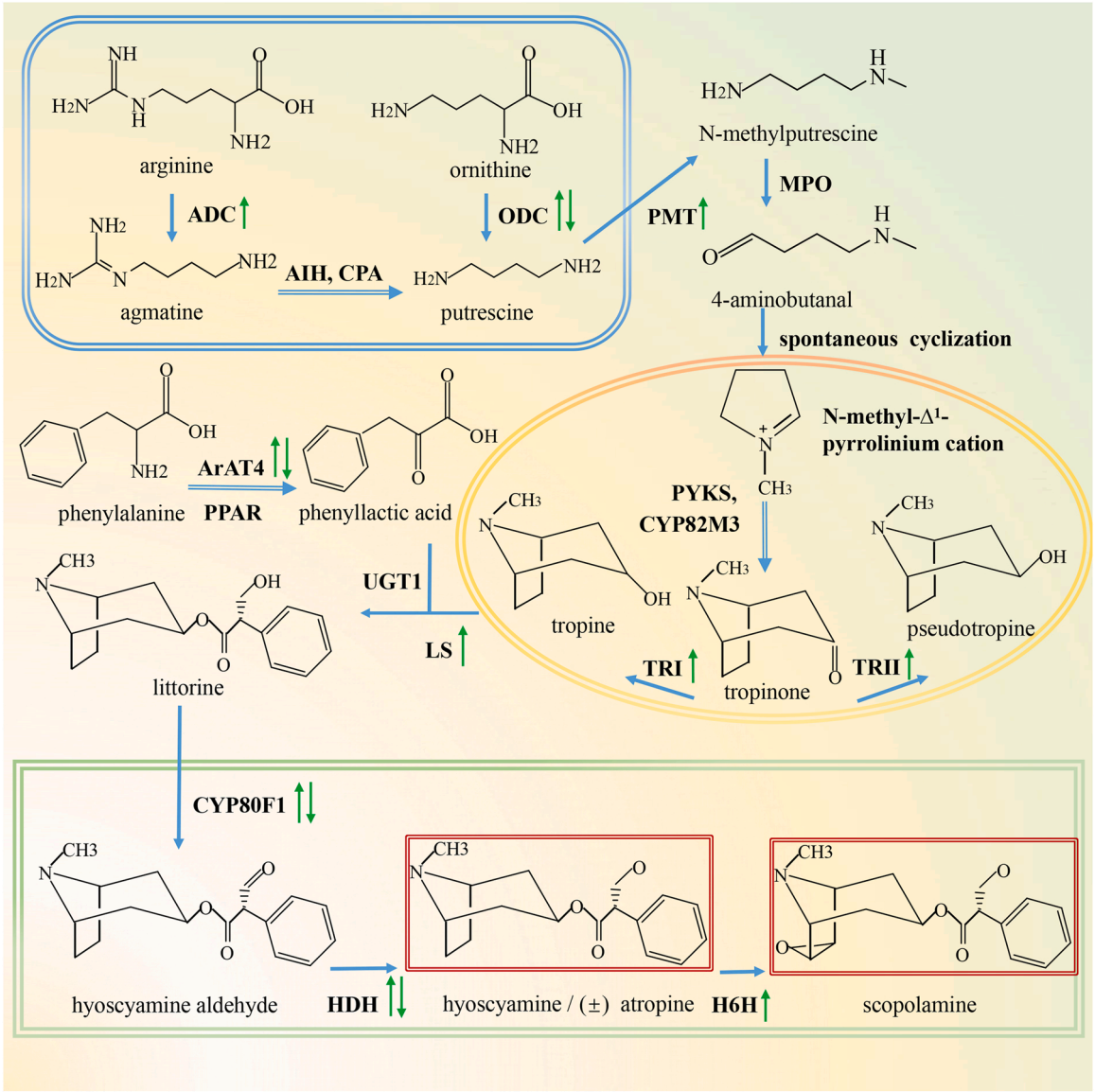


Fig. 2. The biosynthesis pathway of HSA in the Solanaceae. Abbreviations: ADC, arginine decarboxylase; ODC, ornithine decarboxylase; AIH, agmatine iminohydrolase; CPA, N-carbamoylputrescine amidohydrolase; PMT, putrescine N-methyltransferase; MPO, N-methyl-putrescine oxidase; PYKS, pyrrolidine ketide synthase; CYP82M3, tropinone synthase; TRI, tropinone reductase I; TRII, tropinone reductase II; LS, littorine synthase; UGT1, phenyllactate UDP-glycosyltransferase; ArAT4, aromatic amino acid aminotransferase; PPAR, phenylpyruvic acid reductase; CYP80F1, littorine mutase/ monooxygenase; HDH, hyoscyamine dehydrogenase; H6H, hyoscyamine 6β-hydroxylase. Symbols: '⟹ ' represent multi-step reaction steps; '↑' indicates that the gene has been hyperexpression experiments in plants; '↓' indicates that the gene has been performed to suppress or silence expression in plants. Enzyme color scheme: blue box, precursor putrescine biosynthesis; orange circle, tropane core biosynthesis; green box, conversion from littorine to scopolamine; red box, target product.

tropine) have been improved continuously with greater efficiency (Felpin and Lebreton, 2003). In 1974, the production of tropine was facilitated through the polybromo ketone-iron carbonyl reaction of 1, 3-dibromopropan-2-one with methyl 1 H-pyrrole-1-carboxylate (Noyori et al., 1974; Hayakawa et al., 1978). Another novel synthesis route for tropane uses [4 + 2] nitroso cycloaddition of 1,3-cycloheptadienes and 1-chloro-1-nitrosocyclohexane via a Diels-Alder reaction, with a 85% yield at room temperature (Iida et al., 1985). After that, the focus shifted toward the stereochemistry in the synthesis (Drake and Scott, 2018; Rodriguez et al., 2021). Phosphorus-olefin hybrid ligands was used for the synthesis of tropane. In Cu-catalysed reactions, it only had moderate yields, while had better yields in the Hayashi-Miyaura reaction with various substrates (Vlahovic et al., 2013). In addition, a unified synthetic approach was developed for the synthesis of diverse tropane-related scaffolds. The key intermediates are cycloadducts formed by reactions between 3-hydroxy-pyridinium salts and vinyl sulfones or sulfonamides. Diverse scaffolds could be suitable for the design of performance-diverse screening libraries (Lowe et al., 2020).

5. Effects

5.1. Effects of Datura extract

Datura extract play an important role in the treatment of human diseases, the elimination of harmful animal and insects, affecting plant growth and controlling plant diseases, etc. (Fig. 4).

5.1.1. human diseases

Since the TAs of *Datura* extract are mostly plurality muscarinic blockers, they have a sedative effect on the brain and usually serve as an anesthetic, such as ancient Chinese traditional narcotics Mafeisan developed by Hua Tuo in the late eastern Han dynasty of China (about A.

Table 5
The key synthetase genes of HSA synthesis in the genus *Datura*.

Genes	Species	Gene ID/ Protein ID	Length (bp)	Coding sequences	Number of amino acid residues	References
ODC	*Datura stramonium* L.	X87847.1/CAA61121.1	1577	78.1373	431	Michael et al., 1996
ADC1	*Datura stramonium* L.	AJ251898.1/CAB64599.1	2916	433.2607	724	Michael et al., 1999
PMT	*Datura metel* L.	AY327464.1/AAQ94738.1	1156	1.1032	343	Pramod et al., 2003
PMT	*Datura stramonium* L.	AJ583514.1 /CAE47481.1	1035	1.1035	344	Teuber et al., 2007
PMT1	*Datura inoxia* Mill.	AM177609.1/CAJ46253.1	1023	1.1023	340	Teuber et al., 2007
PMT2	*Datura inoxia* Mill.	AM177610.1/CAJ46254.1	1026	1.1026	341	Teuber et al., 2007
PYKS	*Datura stramonium* L.	MN025473.1/QEP99906.1	1472	127.1305	392	Huang et al. (2019)
TRI	*Datura inoxia* Mill.	KJ676865.1/AIN39992.1	822	1.273	273	Qiang et al., 2014
TRI, partial	*Datura metel* L.	AKY01854.1/AKY01854.1	208	1.69	69	Vanitha et al., 2015
TRI	*Datura metel* L.	MW455085.1/QXN57531.1	822	1.273	273	Jia et al., 2021
TRI	*Datura stramonium* L.	AAA33281.1	/	/	273	Nakajima et al., 1993
TRII	*Datura stramonium* L.	AAA33282.1	/	/	260	Nakajima et al., 1993
TR	*Datura stramonium* L.	L20475.1/AAA33280.1	1066	86.892	268	Nakajima et al., 1993
Chain A, TRII	*Datura stramonium* L.	2AE1_A	/	/	260	Nakajima et al., 1993
Chain B, TRII	*Datura stramonium* L.	1IPF_B	/	/	259	Nakajima et al., 1998
Chain A, TRII	*Datura stramonium* L.	1IPF_A	/	/	259	Nakajima et al., 1998
Chain B, TRII	*Datura stramonium* L.	1IPE_B	/	/	259	Nakajima et al., 1998
Chain A, TRII	*Datura stramonium* L.	1IPE_A	/	/	259	Nakajima et al., 1998
Chain B, TRI	*Datura stramonium* L.	1AE1_B	/	/	273	Nakajima et al., 1993
Chain A, TRI	*Datura stramonium* L.	1AE1_A	/	/	273	Nakajima et al., 1993
Chain A, TRII	*Datura stramonium* L.	2AE2_A	/	/	260	Nakajima et al., 1998
Chain B, TRII	*Datura stramonium* L.	2AE2_B	/	/	260	Nakajima et al., 1998
H6H	*Datura metel* L.	AF435417.1/AAQ04302.1	1365	52.1095	347	Pramod et al., 2001
H6H	*Datura metel* L.	6TTO_A	/	/	317	Kluza et al., 2020
H6H	*Datura metel* L.	6TTN_A	/	/	317	Kluza et al., 2020
H6H	*Datura metel* L.	6TTM_A	/	/	317	Kluza et al., 2020
H6H	*Datura stramonium* L.	KR006984.1/ALD59776.1	2660	1.347	347	Qiang et al. (2015)
H6H	*Datura stramonium* L.	KR006982.1/ALD59774.1	1405	1.347	347	Qiang et al. (2015)
CYP80F1	*Datura inoxia* Mill.	AY995182.1	1990	72.1661	529	Natividad et al., 2005

Abbreviations: ODC, ornithine decarboxylase; ADC, arginine decarboxylase; PMT, putrescine N-methyltransferase; PYKS, pyrrolidine ketide synthase; TRI, tropinone reductase I; TRII, tropinone reductase II; H6H, hyoscyamine 6β-hydroxylase; CYP80F1, littorine mutase / monooxygenase.Symbol: '/', no relevant data was retrieved in the NCBI database.

D. 145–208) (Wang, 2014), ancient anesthetics invented by Li shizhen in the Ming dynasty of China (A.D. 1368–1644) (Li, 2016), painkiller extensively used in the Qing dynasty of China (A.D. 1636–1912) (Zhu, 1998) and smoke of *Datura* leaves to alleviate allergies in India (Kamal et al., 2021). Moreover, *Datura* extract shows a good ability in suppression in the production of chemical mediators that stimulate nociceptors and induce pain or inflammation (Asati et al., 2019; Chandan et al., 2021), which can be anti-inflammatory and analgesic (Al-Snafi, 2017; Jaafar et al., 2018) like the edema treament (Muthusamy et al., 2010). In the southern Song Dynasty of China (A.D. 1127–1279), *Datura* extract as a traditional Chinese medicine was used to treat cold and wet feet and sores (Wang, 1990). In contemporary times, Yangjinhua capsules made of *Datura* flower extract have remarkable anti-inflammatory, anti-pruritic and anti-allergy effects and can treat psoriasis (Wang, Xiao et al., 2008). Besides, *Datura* extract is used for wound hearling in Iran for a long time (Kamal et al., 2021). *Datura* extract show very powerful efficacy on the clinical treatment of respiratory (asthma and cough) and digestive diseases (stomach cramps) (Deng et al., 2011). For example, the anti-asthmatic *D. stramonium* cigarette decreases the specific airway resistance (sRaw) of asthmatic patients (Al-Snafi, 2017). Latest animal experiments show that *Datura* extract has an alleviation effects in benzene-induced leukemia (Nasir et al., 2020). *Datura* root, stem and leaf extract have cytotoxic effects on human liver cancer cells and cervical cancer cells, and seed extract have cytostatic effects on human glial tumor cells (Ibrahim et al., 2018; Al-Snafi, 2017; Manzoor et al., 2019; Sharma et al., 2021; Asati et al., 2019). *Datura* extract also has an antioxidant activity that can inhibit cell damage and cure various health diseases, including cancer (Belayneh et al., 2019; Iqbal et al., 2017). These information suggests that *Datura* extract might assist in the treatment of human leukemia and cancer in the future.

5.1.2. harmful animals and insects

Datura extract has good effects on eliminating harmful animal and insects, such as rats (*Rattus norvegicus*), cabbage caterpillart (*Pieris rapae*), *Aedes aegypti* (Swathi et al., 2012), *Tribolium castaneum* (Ali et al., 2017), red imported fire ant (RIFA) workers (*Solenopsis invicta* Buren), etc. *Datura* extract can kill rats through making them sympathetic in a highly excited state (Hong and Yin, 2010) or damaging the liver and gastrointestinal (Hong and Yin, 2010),. The lethality rate of bait poisoning can reach 100.00% (Zhang et al., 2007). *Datura* extract is also well used as insecticide. *Datura* methanol extract has a corrected mortality of 100.00% for cabbage caterpillar (Zhou et al., 2008), a repellent effect of 79.80% for *Tetranychus truncatus* (Zhang et al., 2006), and an obvious toxic effect for housefly (*Musca domestica* L.) with an average mortality rate of 62.78% at the maximum concentration 25.00% (Dong et al., 2011; Attaullah et al., 2020). Compared with the extract of flower, seed and steam, the leaf ethanol extract has the best insecticidal activity of *Helicoverpa armigera* Hubner, resultin in an anti-feeding rate of 56.40% (Cui et al., 2008). Moreover, the leaf extract has high toxic against all life stages of some mites, such as *Spider mites* and *Brevipalpus obovatus* Donnadieu (Bashir et al., 2013; Thevan et al., 2005; Guirado et al., 2001). The lethal rates of dried flowers and leaves extract to RIFA workers can reach 98.67% and 100.00%, respectively (Yang et al., 2019). Besides, the extract combination of *D. stramonium* and *Chenopodium ambrosioides* provides effective control of *Zabrotes subfasciatus* Boheman, resulting in a mortality > 90.00% 120 h after the processing. The combinational effect is better than singleton extract (Bayih et al., 2018). *Datura* extract significantly increases the neurotransmitter acetylcholine, resulting in the over-excited and death of nematodes (Lu et al., 2006). The extract has a certain significant pesticide toxicity on the *Henosepilachna vigintioctopunctata* (Fabricius) larvae, possibly due to the inhibition of certain metabolic enzyme activities, like acetylcholinesterase (AChE), carboxylesterase (CarE) and multifunctional oxidase (MFO) (Li, Yan et al., 2012).

5.1.3. Plant growth

Datura extract can affect seed germination and seedling growth in plant. Many studies show that the inhibition or promotion of seed

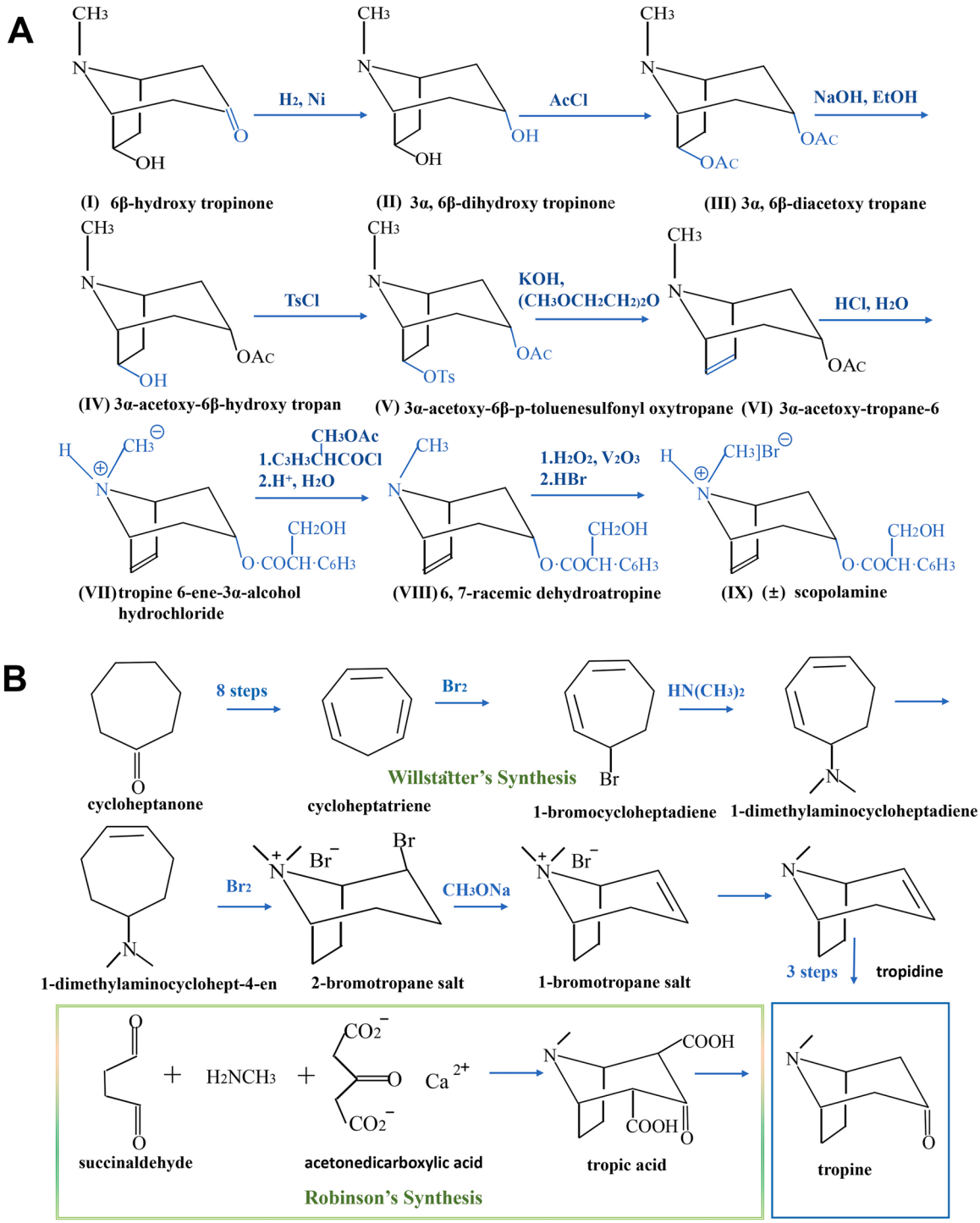


Fig. 3. The chemical synthesis of HSA in the Solanaceae. (A) the chemical synthesis of scopolamine; (B) the chemical synthesis of tropine: the key intermediate in the synthesis of atropine and hyoscyamine. Atropine can be produced with tropine and tropic acid in the presence of hydrogen chloride. Color scheme: blue box, target product; green box, Robinson's synthesis.

germination in agriculture is associated with the concentration of *Datura* extract (Cai and Mu, 2012). For example, low concentration *Datura* extract (< 0.10 mg/mL) promote the germination of corn (*Zea mays* L.) seeds, and the germination is inhibited if the concentration is increased (> 0.10 mg/mL) (Zheng and Li, 2008). Low concentration (0.10 ~ 0.20 mg/mL) promotion and high concentration (0.30 ~ 0.60 mg/mL) inhibition also occur for chickpeas (*Cicer arietinum* L.) and golden beans (*Kongkong kumqua*) (Zheng et al., 2007). However, under the same processing conditions as chickpeas and golden beans, the extract always inhibits the germination of tomato (*Lycopersicon esculentum*) seeds whatever the concentration is and all inhibitions are concentration dependent (Zheng et al., 2007). Of course, it is also possible that *Datura* extract promotes tomato seed germination at unused low concentrations in the experiment, such as a certain concentration of less than 0.1 mg/mL. The reasons for inhibiting seeds germination may be that *Datura* extract may affect the key enzymes required for seed germination, cell division and seed vigor, so that the seed germination process lacks necessary abilities and intermediate products required for

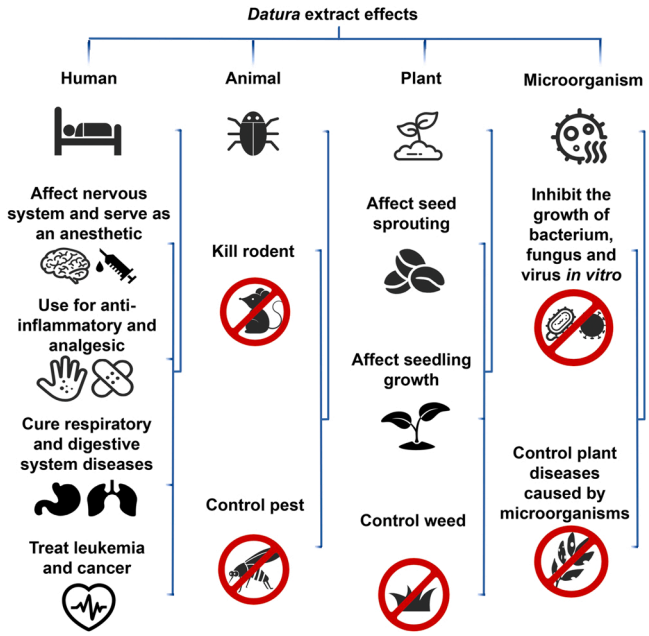


Fig. 4. Effects of *Datura* extract on human beings, animals, plants and microorganisms. Add: Icon from https://www.iconfont.cn.

synthesis and metabolism, thereby reducing seed vigor (Wang et al., 2005; Ma et al., 1999). While there is little information about promoting seeds germination with *Datura* extract, which is required more research. *Datura* extract also affects the seedling growth, mainly reflecting in the growth of roots and stems. The water extract has an significantly inhibitory effect on the root and shoot growth of 4 plants (tomato, pepper (*Capsicum annuum* L.), amaranth (*Amaranthus tricolor* L.) and nepeta (*Nepeta cataria* L.) at two test concentrations (200 and 400 mg/mL), except for nepeta stem with the concentration of 200 mg/mL (Wang, Cheng et al., 2008). This inhibitory effect of *Datura* water extract (100.00 mg/mL) is also observed both in the stems and roots in cucumber (*Cucumis sativus* L.) and wheat (*Triticum aestivum* L.) (Zhou et al., 2009). The "low-promoting and high-inhibiting" phenomenon of *Datura* water extract is also manifested in the root hair growth of soybean (*Glycine max* (Linn.) Merr.) through regulating the cell division. The high-frequency chromosomal aberrations and micronuclei in the meristem cells are induced at high concentration (Cai, 2012). Similar to water extract, *Datura* organic solvents extract also affect the the growth of root and stem. It always shows a significant inhibitory effect both in root and stem at all test concentrations. For example, 100.00 mg/mL *Datura* ethyl acetate extract has the inhibitory effect up to 95.00% on the young stem and radicle of wheat, rape (*Brassica napus* L.), cucumber and sorghum (*Sorghum bicolor* (L.) Moench) (Zhou et al., 2009). The increase of *Datura* ethanol extract concentration reduces the root vigor, protein content, chlorophyll content of corn seedlings and activity of protective enzymes of corn seedlings, so the overall seedling growth shows an inhibitory effect (Zheng and Li, 2008). In addition, 5.00 mg/mL of *Datura* methanol extract can significantly inhibit the seedling growth of some weeds pistia (*Pistia stratiotes* L.), Mikania (*Mikania micrantha* Kunth) and fragrant (*Erigeron bonariensis* L.), etc. (Zhou et al., 2011; Sun et al., 2012), suggesting the possible application as a herbicide. However, the concentration and spray timing of *Datura* extract as a herbicide need to be concerned, as *Datura* extract may inhibit the seedling growth of crops. Aqueous methanol fraction of 20% *Datura* seeds completely inhibited the germination of *Echinochloa colonum*, the major weed of rice, and also significantly reduced the root and shoot growth of rice seedling (Sondhia and Swain, 2002). Herein, how to apply *Datura* extract to promote seed germination and plant growth or as a herbicide, more laboratory and field researches are required. In general, many researches have found that *Datura* extract exhibits low-promoting and high-suppression phenomena and different sensitivities in different organs of plants, which is similar to auxin. Perhaps *Datura* affects the auxin synthesis or the auxin signalling pathway. *Datura* extract may have some main active ingredients which have a similar mode of action like auxin. These issues needs to be further studied.The difference in extraction methods and solvents may affect the results and need to be importantly concerned in furture studies.

5.1.4. Antimicrobial effects

Datura extract shows good application prospects in terms of antimicrobial effects. *In vitro* experiments showed that *Datura* extract has a good inhibition effect on bacteria. Compared with *Escherichia coli* and *Bacillus subtilis*, *Datura* seed extract have the strongest antibacterial activity against *Staphylococcus aureus* and *Micrococcus tetragenus* with minimum inhibitory concentration (MIC) of 2.00 mg/mL (Wang et al., 2009). The extract of root and stem can inhibit the growth of *E. coli* with MIC of 25.00% W/V (Banso and Adeyemo, 2006; Taye et al., 2011). Besides, a ten-fold dilution of 1.00 g/mL *Datura* methanol extract can provide 90.00% inhibition of the *Xanthomonas oryzae pv. oryzae* (Xoo) bacterial colonies (Kagale et al., 2004). *Datura* extract also have inhibition of some other Gram-positive (such as *Bacillus cereus, Staphylococcus epidermidis* and *Staphylococcus saprophyticu*) and Gram-negative bacteria (including *Escherichia coli* and *Salmonella typhi*), which can cause respiratory infections, skin boils, gastrointestinal, biliary system infections, urinary tract infections, etc. (Banso and Adeyemo, 2006; Kaushik and Goyal, 2008; Taye et al., 2011; Khan et al., 1992). *Datura* extract also shows the ability to inhibit fungi in vitro. The 10.00% leaf extract of *D. metel* exhibit the maximum reduction (89.66%) of the mycelial growth of the *Fusarium oxysporum* f. sp. *cubense* (Foc) pathogen (Akila et al., 2011). The inhibition rates of 0.10 mg/mL *Datura* seed extract on the growth of *Phytophthora capsici* and *Fusarium graminearum* reach to 96.91% and 100.00%, respectively (Zhu et al., 2015). Methanolic extract of *D. metel* are found highly effective in suppressing the growth of *Aspergillus fumigatus* (Dabur et al., 2004) and *Macrophomina phaseolina* (Javaid and Saddique, 2012). 20.00% ethanol extract can completely inhibit radial growth of fungi (*Alternaria alternata* (Fr.) Keissler, *Curvularia lunata* (Wakker) Boedijn, *Drechslera oryzae* Breda de Hann (Subramanian and Jain), *Fusarium moniliforme* Sheldon and *Pestalotiopsis guepinii* (Desm.)) isolated from the sick rice (Chowdhury et al., 2018).

In vivo experiments revealed that *Datura* extract show the ability to prevent and control plant diseases. *D. stramonium* extract is effective when mixed with the inoculum, or sprays twice to lower leaf surfaces before inoculation to inhibit Tobacco Mosaic Virus (TMV) disease in *Nicotiana tabaccum* L. (Apablaza and Bernier, 1972). Spraying with 0.10 g/L methanol leaf extract of *D. metel* in pre- and post-inoculation reduces sheath blight disease 53.00% and 41.00% in rice, respectively (Kagale et al., 2004). Extract of *D. metel* (25 g/L) applies as a prophylactic spray reduced the frequency of late leaf spot (LLS) lesions and rust pustules by 65.00–74.00% compared with controls, and the application of extract prior to inoculation better limits the symptom development than post-inoculation (Kishore and Pande, 2005).

The combination of *Datura* extract and other substances into herbal preparations might open up a new way for its antibacterial effects. For example, a herbal preparation containing *Dalbergia sissoo* and *D. stramoium* with cow urine solvent (DSDS) has better antibacterial potential against pathogenic strains of gram-positive and gram-negative bacteria, comparing to methanol or water extract as solvent of *Dalbergia sissoo* and *D. stramoium* extract (Yadav et al., 2008). In addition, Environment factors have an impact on the antibacterial effect of *Datura*. About 2–3 h UV irradiation (245 nm) made the *Datura* extract lose the antibacterial activity for *Pseudomonas marginalis*, *Stephylococcus aureus* and *Pseudomona aeruginosa consecutive* (Abd-Allah et al., 2018). Therefore, when it's applied to prevent and control plant diseases, it must consider the environment factors and the concentration of *Datura*

extract, which also affects plant growth.

5.2. Effects of HSA

HSA are the most studied TAs. As the antagonists of the muscarinic (M-) acetylcholine (ACh) receptors, they play important roles in regulating the central nervous system (CNS). Meanwhile, they play a part in the digestive system, respiratory system, ophthalmology, cardiovascular field, etc. (Fig. 5).

5.2.1. Hyoscyamine

Hyoscyamine is a similar analgesic to atropine and is used in the clinical treatment of digestive, nervous system, cardiovascular diseases, etc. Hyoscyamine can significantly reduce the pressure of the lower esophageal sphincter and the compression pressure of the esophagus and is a potential medicine for the oesophago-spastic disorder (Allen et al., 1987). Oral hyoscyamine can reduce abdominal discomfort and colonic spasm during a barium enema, which has lower uncomfortableness and adverse effects compared with intravenous glucagon (Bova et al., 1993). Studies have also shown that hyoscyamine is an economical alternative to glucagon hypotonic gastroenterography (Moeller et al., 1992). Hyoscyamine is one of the only two non-combination antispasmodics available in the USA by prescription, which is anticholinergic and therefore may reduce diarrhea and urgency. In addition, hyoscyamine can be used as an anticholinergic drug in the treatment of Parkinson's disease and genitourinary symptoms (Srimathi et al., 2018). Bradyarrhythmias can also be treated with hyoscyamine, but persistent bradyarrhythmias still require pacemaker placement after hyoscyamine treatment (Khan et al., 2017).

For other diseases, a study showed that R-(+)-hyoscyamine can produce antinociceptive effects through cholinergic mechanisms in both rodents and rabbits by injection, and the analgesic intensity of R-(+)-hyoscyamine was comparable to that of morphine (2 mg/kg) and minaprine (15 mg/kg) by subcutaneous injection (Ghelardini et al., 1999). Hyoscyamine can affect the growth and reproduction of the pathogen, causing the electrolyte leakage of the mycelium of *Magnaporthe grisea* and *Rhizochaea solanum*, thereby inhibiting the spore germination and the formation of appressorium (Abdel-Motaal et al., 2010).

5.2.2. Scopolamine

Since scopolamine was isolated from *Scopolia japonica* in 1850 (Yamada and Tabata, 1997), it has been detected in more and more Solanaceae family plants. *Datura* is one of the best resource plants to extract scopolamine (Vitale et al., 1995). Now it is a very important medicine with extensive clinical applications.

5.2.2.1. Application in CNS. Scopolamine is a competitive antagonist of muscarinic ACh receptors that potently affect the cognition processes, sensory functions, stress responses, etc., thus there are widespread applications in the field of the CNS, such as the curation of motion sickness, the treatment of depression, the usage as anesthetics, the induction of disease models, etc.

As an anticholinergic, scopolamine is one of the most common pharmacological agents for motion sickness. It can interfere the transmission of vestibular input to the CNS, which suppresses the urge to vomit activated by motion sickness (Spinks and Wasiak, 2011). During the Second World War, scopolamine has been widely applied in the treatment of motion sickness (M, 2015). In 1981, a technology, transdermal therapeutic systems (TTS), was developed (Kohnen-Johannsen and Kayser, 2019), and then transdermal scopolamine patches (a patch system containing 1.5 mg scopolamine) were invented and quickly used for preventively or long-term therapy in motion sickness (Grøntved et al., 1988). Scopolamine patch is more recommended than oral cinnarizine tablet in the treatment of motion sickness among naval crew and sea travelers, due to its high efficacy, few side effects and convenience (Gil et al., 2012). However, there are some cases of adverse effects after using scopolamine patch, such as the deterioration of cognitive function and the severe alteration of the mental status of a four-year-old boy after using scopolamine patch (Lin et al., 2011). There is another case with withdrawal syndrome occurring after years of occasional use of transdermal scopolamine patch (Manno et al., 2015). Therefore, it is essential to regulate and know the proper use of scopolamine patch as it is Over The Counter (OTC) medication, and serious adverse effects may occur when misused (Lim et al., 2008). Another potential way to relieve motion sickness symptoms is intranasal scopolamine, without seeing significant sleepiness or cognitive impairment after assessing 8 subjects. Here, more samples are required (Stankovic et al., 2019).

Scopolamine attracts more and more attention due to its rapid and

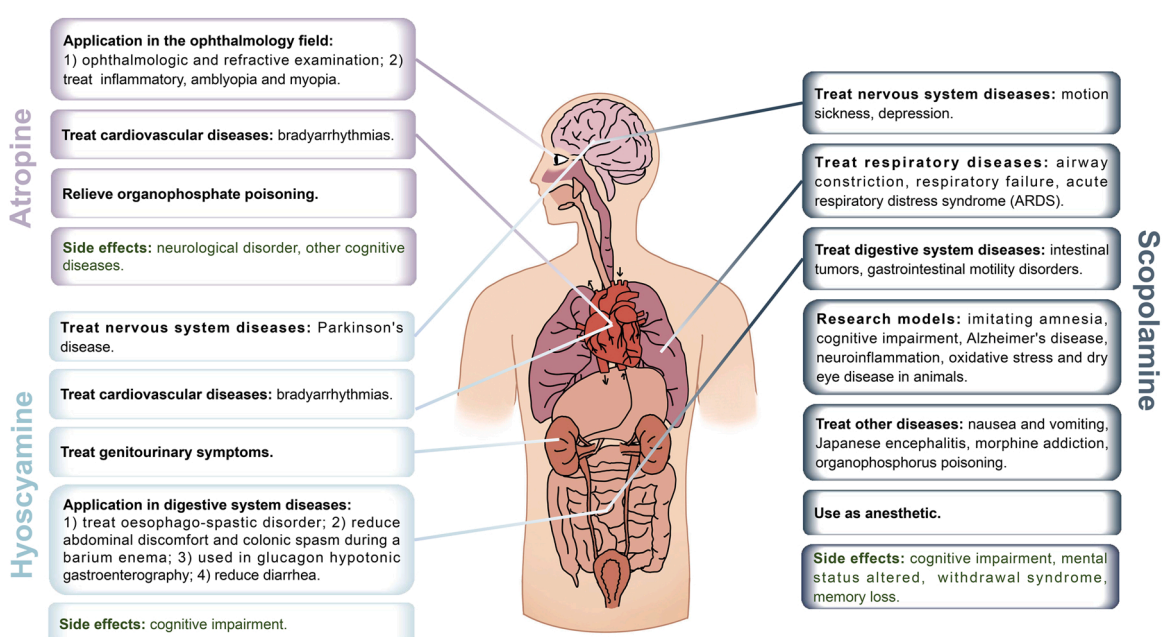


Fig. 5. The effect and side effect of HSA on human.

sustained antidepressant activities. Scopolamine is effective in reducing depressive symptoms and as an antianxiety drug in patients with clinical depression and bipolar disorder (Furey and Drevets, 2006; Furey et al., 2010). There are different explanations about the mechanisms of treating depression with scopolamine. It is revealed by preclinical studies that the increase of glutamate neurotransmission and activation of the mechanistic target of rapamycin complex 1 signaling in the prefrontal cortex are the reasons to cause the rapid antidepressant responses to scopolamine (Voleti et al., 2013; Li et al., 2010). Another study suggests that the release of activity-dependent brain-derived neurotrophic factor (BDNF) plays a vital role in the rapid antidepressant effect of scopolamine (Ghosal et al., 2018). Activation of the norepinephrine system might be involved in the process as well (Pałucha-Poniewiera et al., 2017). In addition, the scopolamine patch only has a weak effect on emotional cognition, indicating that the available effective dose of scopolamine from the patch may not be enough to have a feasible antidepressant function (Bukala et al., 2019). Therefore, the treatment of scopolamine for depression needs further research in mechanism and how to use it properly.

In clinical operation, scopolamine is well known for its good anesthetic effect. In the early 20th century, scopolamine was successfully used as an anesthetic drug to make the expectant mother fall in "twilight sleep" during childbirth, along with morphine and chloroform (Foley, 2006). However, these women in twilight sleep lost the memory of the birth process, which indicates that scopolamine has an effect on diminishing consciousness in specific doses. The clinical experiment of scopolamine in the cesarean section under general anesthesia suggested a single intravenous injection of scopolamine at 5 μg/kg body weight was clinically useful with no significant residual effect, while both intramuscular injection (10 μg/kg) and oropharyngeal injection (35 μg/kg) caused too strong side effects (Renner et al., 2005). In addition, Another study showed that median and interquartile range serum scopolamine levels were 1.9 and 2.1 ng/mL in non-fatal cases of diminished consciousness, respectively (Barceló et al., 2020).

In recent years, scopolamine-induced disease research models have become a hotspot. Because scopolamine can have damage on learning and memory via activation of the cholinergic system and anti-neuroinflammation (Choi et al., 2021), scopolamine can be used in many studies as the drug that mimics the illness of memory lost to explore the effects of other drugs in the amnesia, cognitive impairment, and other neuronal damage in mouse (*Mus musculus*), *C. elegans* and rat, etc. (Ehsani et al., 2018; Chen et al., 2018; Momtazi-Borojeni et al., 2017; Ban et al., 2020). Scopolamine also can cause dysregulation of cholinergic signals in the brain (Klinkenberg and Blokland, 2010) and increase amyloid-β deposition (Win Ning and Keng Yoon, 2020), which are the main reasons for Alzheimer's pathology. Thus scopolamine is often used as an experimental model for Alzheimer's disease (Win Ning and Keng Yoon, 2020; Godyń et al., 2021; Aghajanzadeh et al., 2020) to evaluate the treatment ability of other drugs (like cinnamic acid hybrids, N-benzylpyrrolidine and 1,3,4-oxadiazole, etc.) (Choubey et al., 2021; Wang, Shi et al., 2021). Scopolamine can cause neuroinflammation and oxidative stress, and acts as a model in the study of its mechanism and treatment (Iqbal et al., 2020; Maricarmen et al., 2020). Besides, scopolamine can imitate dry eye disease in mouse and rabbit (*Oryctolagus cuniculus*) by injection and is used as a model to explore other drugs' efficacy of treating (Wang, Zuo et al., 2021).

5.2.2.2. Respiratory diseases. Scopolamine is effective in the treatment of respiratory diseases. Some nerve agents can cause cholinergic syndrome-like respiratory failure by inhibiting the acetylcholinesterase and promoting a rapid accumulation of the neurotransmitter ACh. As scopolamine is an anticholinergic agent as a blocker of muscarinic ACh receptors, it has the potential to alleviate the cholinergic syndrome. It is demonstrated that scopolamine can treat airway constriction in the rat precision-cut lung slices introduced by exposing to nerve agent VX, thus playing a role in the treatment of respiratory failure (Wigenstam et al., 2021). Based on mechanical ventilation treatment, scopolamine combined with ulinastatin in the treatment of acute respiratory distress syndrome (ARDS) is effective, safe and reliable, and may provide a new method (Hongshun and Zhifeng, 2016). Scopolamine can also be used to cure pediatric persistent pneumonia with antibacterial, antiviral, cough and phlegm treatment (Guihua, 2013). Besides, it can treat acute toxic pulmonary edema combined with dexamethasone (Weijun, 2015).

5.2.2.3. Digestive diseases. Continual use of scopolamine to treat gastrointestinal motility disorders usually has adverse effects on the CNS (Pan and Han, 2004), indicating whenever the side effects of scopolamine must be considered. Meanwhile, the quaternary ammonium derivative of scopolamine (scopolamine butylbromide, NBS) is suggested to attenuate the formation and growth of intestinal tumors (Raufman et al., 2011), which does not cross the blood-brain barrier, and thus does not cause central nervous system side effects (Alleva and Bignami, 1985; Estapé and Steckler, 2002).

5.2.2.4. Other diseases. In addition to the above diseases, transdermal scopolamine was associated with a significant reduction in postoperative nausea and vomiting by early and late patch application 24 h after the onset of anesthesia (Apfel et al., 2010; Antor et al., 2014). Scopolamine is also used in the treatment of Japanese encephalitis morphine (Kumar et al., 2020) and addiction in humans (Xiang et al., 2006). Besides, scopolamine can treat poisoning with organophosphorus compounds due to its smooth muscle relaxing effect (Marquart et al., 2019).

5.2.3. Atropine

Atropine was first isolated from *Atropa belladonna* in 1833 (Yamada and Tabata, 1997). By the end of the 19th century, the stereochemical relationship between atropine and hyoscyamine was elucidated and found that atropine is the racemate of hyoscyamine (Lossen, 1864). Hyoscyamine is easy to turn racemic into atropine, while atropine is very stable over time, so it is used more often in therapeutic areas than hyoscyamine.

5.2.3.1. Ophthalmology. Atropine has been widely used in the field of ophthalmology, ranging from the diagnosis of some ophthalmic diseases to the treatment of amblyopia, myopia, inflammation and other diseases. Atropine-induced pupil astigmatism and ciliary palsy are important means of ophthalmologic examination and refractive examination (García Del Valle and Alvarez-Lorenzo, 2021). Atropine can be applied to the therapy of acute inflammatory processes: 1% atropine is the first-choice drug to avoid pain, rebuild the blood-aqueous barrier and prevent deterioration by fixing the iris and ciliary body (Agrawal et al., 2010). Atropine can also treat amblyopia as a substitute to spectacles correction and patching from the age of three (Osborne et al., 2018; Repka et al., 2014). Extensive clinical evidence has proved the effect of atropine eye drops in myopia controlling progression, though the exact mechanism and location of atropine's action are still unclear (Upadhyay and Beuerman, 2020). In trials conducted at higher concentrations (often 1%), atropine slowed axial elongation by 70–94% but has been associated with side effects such as photophobia (Tran et al., 2018). The convenience of atropine in penetrating ocular tissue is a double-edged sword. The wide use of atropine in eye drops but its nonspecific distribution leads to a variety of adverse effects (García Del Valle and Alvarez-Lorenzo, 2021). So there are concerns about the adverse effects in cognition, for atropine is also a medicine with anticholinergic properties which has significant negative effects on cognition and physical function (Fox et al., 2014), and there is a case of accidental poisoning due to atropine eye drops, resulting in a severe neurological disorder resembling an acute stroke (Faivre et al., 2012). Consequently, there is a need to further understand the mechanism of atropine's action and

reduce its adverse effects on other parts of the body.

5.2.3.2. Organophosphate poisoning. Organophosphorus pesticides inhibit acetylcholinesterase, which results in the accumulation of acetylcholine and overstimulation of acetylcholine receptors in synapses of the autonomic nervous system, CNS, and neuromuscular junctions, causing organophosphate poisoning (Eddleston et al., 2008). Through blocking the effect of acetylcholine on the parasympathetic nerve and the M receptor of the central nervous system, atropine can quickly relieve organophosphate poisoning, including the M-like symptoms and part of the toxic symptoms of the CNS (Hao, 2017). Meanwhile, atropine can inhibit the secretion of a variety of glands and make coma patients wake up. Herein, atropine, as the first-line antidote and oximes in combination with atropine, are products for the treatment of organophosphate poisoning approved by the US Food and Drug Administration (Alozi and Rawas-Qalaji, 2020).

5.2.3.3. Other diseases. Bradyarrhythmia (bradycardia) is a slow heart rate of fewer than 60 beats per minute (Kossmann, 1953), and atropine is used for its episodes (Karim et al., 2020). In acute cases of bradyarrhythmias, symptomatic patients can be treated with atropine (Barstow and Mcdivitt, 2017). Atropine is recommended with a dose of 0.5 mg every 3–5 min, in small doses if needed (St-Onge et al., 2017), which is based on the consideration that the treatment may be temporarily effective, easily available, feasible, inexpensive and low-risk (Gay et al., 1986; Strubelt, 1984).

Atropine has a good therapeutic effect on animal diseases. Atropine has the characteristics of quick curative effect and a high cure rate in the treatment of piglet yellow and white dysentery, which is worthy of use by veterinarians (Guangxiao et al., 2013). Atropine can also treat infectious gastroenteritis, epidemic diarrhea, piglet paratyphoid and other intestinal diseases (Xiaoping, 2012). When the animal body appears parasitic disease, timely hypodermic injection of atropine sulfate can relieve the symptom, and studies showed that subcutaneous injections of atropine sulfate are effective in the treatment of gastrointestinal torsion (Rongzhen, 2012). Besides, atropine can be used to construct slow transit constipation model rats (Xu et al., 2021).

6. Conclusion

The explore of *Datura* plants has evolved from the simple application of extract in the ancient era to the study of synthesises and effects of individual bioactive ingredients from extract to date (Fig. 1). HSA are detected in all species in *Datura* (Table 4) by diversified extraction methods developed to date (Table 3). However, The extraction methods and HSA content in *Datura* is expected to be further improved in terms of solvents and new technologies, such as genetic transformation, treating with nanoparticles and chromosome doubling, etc. Synthetic research related to HSA has been carried out for more than 100 years with fruitful results. The completed biosynthesis route has been illustrated clearly (Fig. 2), and the new technology of *de novo* synthesis is on the rise recently. The successfully total biosynthesis of hyoscyamine and scopolamine via engineered yeast suggests that the supply of medicinal HSA can be complemented or replaced by the in vitro biosynthesis, and microbial biosynthesis platforms can facilitate the discovery of TA derivatives as new therapeutic agents for more diseases (Srinivasan and Smolke, 2020). However, the regulation of HSA biosynthesis may vary from species to species. Except for this, researches on metabolic engineering combined genome sequencing should also pay attention to the common overexpression of multiple genes in biosynthesis and related regulatory genes. Great progress has been made in chemical synthesis (Fig. 3), while, some steps still face the problems of low yields, harsh process conditions and complicated operations, which are not suitable for industrial production. In future research on the chemical synthesis of HSA, in addition to explore new efficient synthetic routes, it is also necessary to improve the reaction conditions to make them suitable for modern requirements of the pharmaceutical factories. With the in-depth study of genus *Datura*, *Datura* extract and HSA both can regulate physiological activities of various animal organs by inhibiting M-type anticholinergic receptors in different parts, thereafter having good effects on human diseases (Figs. 4–5), and the mechanism of treating the disease needs to be better understood. Advances in plant growth, antibacterial, anti-insects, weeding etc. show *Datura* has the potential for application in agriculture, while the field experiment is urgently needed. Both *Datura* extract and HSA function exhibit a dose-dependent type, herein, we should focus on the dose of side effects during the treatment of human disease and correctly use the "low promotion and high inhibition" in plant growth.

Author contributions

ZW S, WJ Z, ZM Z, ZW X and P D work together to write the initial drafts of manuscript. ZW S, WJ Z, ZM Z, ZW X, ZL Z and P D prepare the figures and tables. P D, SY L and ZL Z revise the manuscript.

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.

Acknowledgements

This work was supported by National College Student Innovation Training Program, China (202110611106), Chongqing Natural Science Foundation, China (cstc2019jcyj-msxmX0127), Research Project on Teaching Reform of Chongqing University, China (2019Y61), the Youth Innovative Talents Training Project of Chongqing, China (CY220140, CY220105) and the Open Project Program of Panxi Crops Research and Utilization Key Laboratory of Sichuan Province, China (No. SZKF2109).

References

Abd-Allah, A.S., Mukhlif, F.H., Al-Shaheen, Y. a M.M.R., et al., 2018. The effect of uv irradiation on antimicrobial activity of water extract from Datura metel L. IOP Conf. Ser.: Mater. Sci. Eng. 454, 012109.

Abdel-Motaal, F.F., El-Zayat, S.A., Kosaka, Y., et al., 2010. Antifungal activities of hyoscyamine and scopolamine against two major rice pathogens: *Magnaporthe oryzae* and *rhizoctonia solani*. J. Gen. Plant Pathol. 76, 102–111.

Afewerki, S., Wang, J.-X., Liao, W.-W., et al., 2019. Chapter three - the chemical synthesis and applications of tropane alkaloids. In: Hans-Joachim, Knölker (Ed.), The alkaloids: Chemistry and biology. Academic Press.

Aghajanzadeh, M., Andalib, S., Danafar, H., et al., 2020. The effect of baicalein-loaded y-shaped miktoarm copolymer on spatial memory and hippocampal expression of *dhcr24*, *seladin* and *sirt6* genes in rat model of alzheimer. Int. J. Pharm. 586.

Agrawal, R.V., Murthy, S., Sangwan, V., et al., 2010. Current approach in diagnosis and management of anterior uveitis. Indian J. Ophthalmol. 58, 11–19.

Ajungla, L., Patil, P.P., Barmukh, R.B., et al., 2009. Influence of biotic and abiotic elicitors on accumulation of hyoscyamine and scopolamine in root cultures of *Datura metel* L. Indian J. Biotechnol. 8, 317–322.

Akila, R., Rajendran, L., Harish, S., et al., 2011. Combined application of botanical formulations and biocontrol agents for the management of *fusarium oxysporum* f. *Sp*. Cubense (Foc.) causing fusarium wilt Banan., Biol. Control 57, 175–183.

Ali, K., Sagheer, M., Mansoor Ul, H., et al., 2017. Impact of extracts of Azadirachta indica and Datura inoxia on the esterases and phosphatases of three stored grains insect pests of economic importance. Pak. J. Agric. Sci. 54, 71–81.

Alinejad, S., Sarabi, V., Bakhtvari, A.R.S., et al., 2020. Variation in physiological traits, yield and secondary metabolites of jimsonweed (*Datura stramonium* L.) under different irrigation regimes and nutrition systems. Ind. Crops Prod. 143, 111916.

Allen, M., Mellow, M., Robinson, M.G., et al., 1987. Comparison of calcium channel blocking agents and an anticholinergic agent on oesophageal function. Aliment. Pharmacol. Ther. 1, 153–159.

Alleva, E., Bignami, G., 1985. Development of mouse activity, stimulus reactivity, habituation, and response to amphetamine and scopolamine. Physiol. Behav. 34, 519–523.

Alozi, M., Rawas-Qalaji, M., 2020. Treating organophosphates poisoning: Management challenges and potential solutions. Crit. Rev. Toxicol. 50, 764–779.

Al-Snafi, A., 2017. Medical importance of *Datura fastuosa* (syn: *Datura metel*) and *Datura stramonium* -a review. IOSR J. Pharm. 7, 43–58.

An, X., 2012. Callus culture and scopolamine analysis of young stem of *Datura*, Master. Liaoning Normal University.

Antor, M.A., Uribe, A.A., Erminy-Falcon, N., et al., 2014. The effect of transdermal scopolamine for the prevention of postoperative nausea and vomiting. Front. Pharmacol. 5.

Apablaza, G.E., Bernier, C.C., 1972. Inhibition of tobacco mosaic virus infection by plant extracts. Can. J. Bot. 50, 1473–1478.

Apfel, C.C., Zhang, K., George, E., et al., 2010. Transdermal scopolamine for the prevention of postoperative nausea and vomiting: A systematic review and meta-analysis. Clin. Ther. 32, 1987–2002.

Asati, V., Agarwal, R., Gupta, R., et al., 2019. Anti-inflammatory activity of seeds extract of *Datura stramonium* against carrageenan induced paw edema on albino wistar rats. J. Pharm. Biol. Sci. 7, 41–46.

Attaullah, Zahoor, M.K., Zahoor, M.A., et al., 2020. Insecticidal, biological and biochemical response of Musca domestica (diptera: Muscidae) to some indigenous weed plant extracts. Saudi J. Biol. Sci. 27, 106–116.

Babaali, D., Roeb, J., Hammache, M., et al., 2017. Nematicidal potential of aqueous and ethanol extracts gained from *Datura stramonium*, *d. Innoxia* and *d. Tatula* on *meloidogyne incognita*. J. Plant Dis. Prot. 124, 339–348.

Bachheti, R.K., Rai, I., Mishra, V.K., et al., 2018. Antioxidant and antimicrobial properties of seed oil of *Datura metel*. J. Environ. Biol. 39, 182–188.

Ban, J.Y., Park, H.K., Kim, S.K., 2020. Effect of glycyrrhizic acid on scopolamine-induced cognitive impairment in mice. Int Neurourol. J. 24, S48–S55.

Banso, A., Adeyemo, S., 2006. Phytochemical screening and antimicrobial assessment of *Abutilon mauritianum*, *bacopa monnifera* and *Datura stramonium*. Biokemistri 18, 39–44.

Barceló, B., Gomila, I., De-Castro-Ríos, A., et al., 2020. Diminished consciousness in a woman following an unsuspected scopolamine overdose. J. Anal. Toxicol. 45, e7–e14.

Barelay, 1959. New considerations in an old genus, 18. Datura, Botanical Museum Leaflets (Harvard University, pp. 245–272.

Barstow, C., Mcdivitt, J.D., 2017. Cardiovascular disease update: bradyarrhythmias. FP Ess. 454, 18–23.

Bashir, M.H., Gogi, M.D., Ashfaq, M., et al., 2013. The efficacy of crude aqueous extracts of some plants as grain protectants against the stored grain mite, *rhizoglyphus* tritici. Turk. J. Agric. For. 37, 585–594.

Bayih, T., Tamiru, A., Egigu, M.C., 2018. Bioefficacy of unitary and binary botanical combinations against mexican bean weevil, *Zabrotes subfasciatus* (coleoptera: Chrysomelidae). Int. J. Trop. Insect Sci. 38, 205–215.

Bedard, A.C., Longstreet, A.R., Britton, J., et al., 2017. Minimizing e-factor in the continuous-flow synthesis of diazepam and atropine. Bioorg. Med. Chem. 25, 6233–6241.

Bedewitz, M.A., Gongora-Castillo, E., Uebler, J.B., et al., 2014. A root-expressed l-phenylalanine:4-hydroxyphenylpyruvate aminotransferase is required for tropane alkaloid biosynthesis in *atropa belladonna*. Plant Cell 26, 3745–3762.

Bejeuhr, G., 1995. Hagers handbuch der pharmazeutischen praxis. Pharm. Unserer Zeit 24, 81–84.

Belayneh, Y.M., Birhanu, Z., Birru, E.M., et al., 2019. Evaluation of in vivo antidiabetic, antidyslipidemic, and in vitro antioxidant activities of hydromethanolic root extract of *Datura stramonium* l. (solanaceae). J. Exp. Pharmacol. 11, 29–38.

Benítez, G., March-Salas, M., Villa-Kamel, A., et al., 2018. The genus *Datura* l. (solanaceae) in mexico and spain – ethnobotanical perspective at the interface of medical and illicit uses. J. Ethnopharmacol. 219, 133–151.

Berkov, S., Pavlov, A., 2004. A rapid densitometric method for the analysis of hyoscyamine and scopolamine in solanaceous plants and their transformed root cultures. Phytochem. Anal. 15, 141–145.

Berkov, S., Zayed, R., Doncheva, T., 2006. Alkaloid patterns in some varieties of *Datura stramonium*. Fitoterapia 77, 179–182.

Boros, B., Farkas, Á., Jakabová, S., et al., 2010. Lc-ms quantitative determination of atropine and scopolamine in the floral nectar of *Datura* species. Chromatographia 71, 43–49.

Bova, J.G., Jurdi, R.A., Bennett, W.F., 1993. Antispasmodic drugs to reduce discomfort and colonic spasm during barium enemas: Comparison of oral hyoscyamine, i.V. Glucagon, and no drug. Am. J. Roentgenol. 161, 965–968.

Bukala, B.R., Browning, M., Cowen, P.J., et al., 2019. Overnight transdermal scopolamine patch administration has no clear effect on cognition and emotional processing in healthy volunteers. J. Psychopharmacol. 33, 255–257.

Bye, R., Sosa, V., 2013. Molecular phylogeny of the jimsonweed genus *Datura* (solanaceae). Syst. Bot. 38, 818–829.

Cai, S., 2012. Morphplogical and anatomical response of seedling root of *Glycine max* (L.) merrill to the alleopathic stress of aqueous extracts of *Datura stramonium* L., Master. Northwest A&F University.

Cai, S., Mu, X., Mao, L., et al., 2012. Young root growth and cell division of soybean stressed by aqueous leachate of *Datura stramonium* leaves. Acta Bot. Boreal. -Occident. Sin. 32, 117–123.

Cai, S.L., Mu, X.Q., 2012. Allelopathic potential of aqueous leaf extracts of *Datura stramonium* l. On seed germination, seedling growth and root anatomy of *Glycine max* (L.) merrill. Allelopath. J. 30, 235–246.

Chandan, G., Kumar, C., Chibber, P., et al., 2021. Evaluation of analgesic and anti-inflammatory activities and molecular docking analysis of steroidal lactones from *Datura stramonium* L. Phytomedicine 89, 153621.

Chen, B.H., Ahn, J.H., Park, J.H., et al., 2018. Effects of scopolamine and melatonin cotreatment on cognition, neuronal damage, and neurogenesis in the mouse dentate gyrus. Neurochem. Res. 43, 600–608.

Chen, J., Zhang, F., Zhang, R., 2019. Determination of hyoscyamine and scopolamine in *Datura* by lc-ms/ms. J. Jinggangshan Univ. (Nat. Sci. Ed.) 40, 92–95.

Chen, P., Fu, C., Wu, Z., et al., 2017. Research progress of scopolamine pharmaceutical intermediates. Anhui Chem. Ind. 43, 1–4.

Cheng, Y., Wang, H., Duan, J., et al., 2011. A preliminary study on allelopathic effects of invasive weed *Datura stramonium* l. On cultivated plants. J. Henan Agric. Univ. 45, 215–219.

Choi, J.-H., Lee, E.-B., Jang, H.-H., et al., 2021. Allium hookeri extracts improve scopolamine-induced cognitive impairment via activation of the cholinergic system and anti-neuroinflammation in mice. Nutrients 13, 2890.

Choubey, P.K., Tripathi, A., Tripathi, M.K., et al., 2021. Design, synthesis, and evaluation of n-benzylpyrrolidine and 1,3,4-oxadiazole as multitargeted hybrids for the treatment of alzheimer's disease. Bioorg. Chem. 111, 104922.

Chowdhury, P., Bashar, M.A., Shamsi, S., 2018. In vitro evaluation of fungicides and plant extracts against pathogenic fungi of two rice varieties. Bangladesh J. Bot. 44, 251–259.

Cui, Z., 2009. Study on insecticidal activity of extracts from *Datura metel* L. Huazhong Agricultural University.

Cui, Z., Chen, G., and Wang, M. 2008. Preliminary reaseareh of insecticidal activity of *Datura metel* L. central china insect research. In *2008 Annual Academic Conference of Entomological Society of Three Provinces in Central China (Hubei, Hunan, Henan)* , 8. Xianning, Hubei, China.

Dabur, R., Singh, H., Chhillar, A.K., et al., 2004. Antifungal potential of indian medicinal plants. Fitoterapia 75, 389–391.

Delayno, M. a D., 1994. Quantitative-determination of scopolamine in *Datura-ferox* L. *(chamico)* seeds from different agentine regions. An. De. La Asoc. Quim. Argent. 82, 455–460.

Deng, Z., Luo, C., Liu, B., et al., 2011. Development and utilization of medicinal value on *Datura stramonium* l. Prog. Mod. Biome*dicine* 11, 1394–1398.

Diab, S., Mytis, N., Boudouvis, A.G., et al., 2019. Process modelling, design and technoeconomic liquid-liquid extraction (lle) optimisation for comparative evaluation of batch vs. Contin. Pharm. Manuf. atropine, Comput. Chem. Eng. 124, 28–42.

Dong, C., Wu, Q., Xu, H., et al., 2011. Insecticidal activity of the extracts from 40 species of plants in hainan island against *Musca domestica* linaeus. Acta Agric. Univ. Jiangxiensis 33, 476-81+87.

Dräger, B., 2006. Tropinone reductases, enzymes at the branch point of tropane alkaloid metabolism. Phytochemistry 67, 327–337.

Drake, L.R., Scott, P.J.H., 2018. Dark classics in chemical neuroscience: Cocaine. Acs Chem. Neurosci. 9, 2358–2372.

Eddleston, M., Buckley, N.A., Eyer, P., et al., 2008. Management of acute organophosphorus pesticide poisoning. Lancet 371, 597–607.

Ehsani, S., Akbari, E., Ardeshiri, M.R., 2018. The effect of intracerebroventricular administration of insulin on memory impairment-induced by scopolamine in male rats. Physiol. Pharmacol. 22, 240–246.

Estapé, N., Steckler, T., 2002. Cholinergic blockade impairs performance in operant dnmtp in two inbred strains of mice. Pharmacol. Biochem. Behav. 72, 319–334.

Faivre, A., Mounier, C., Gaillard, T., et al., 2012. Intoxication grave à l'atropine mimant une urgence neurovasculaire. Rev. Neurol. 168, 450–453.

Felpin, F.X., Lebreton, J., 2003. Recent advances in the total synthesis of piperidine and pyrrolidine natural alkaloids with ring-closing metathesis as a key step. Eur. J. Org. Chem. 2003, 3693–3712.

Fodor, G., Koczka, K., Lestyán, J., 1956. 287. Stereochemistry of tropane alkaloids. Part ix. Selective quaternisation of tropan-3α-ol and tropan-3β-ol and of their derivatives. J. Chem. Soc. (Resume) 1411–1417.

Foley, P., 2006. *Duboisia myoporoides*: The medical career of a native australian plant. Hist. Rec. Aust. Sci. 17, 31–69.

Fox, C., Smith, T., Maidment, I., et al., 2014. Effect of medications with anti-cholinergic properties on cognitive function, delirium, physical function and mortality: A systematic review. Age Ageing 43, 604–615.

Friedman, M., Levin, C.E., 1989. Composition of jimson weed (*Datura stramonium*) seeds. J. Agric. Food Chem. 37, 998–1005.

Fu, W., 2020. Effect of *rol* gene expression in *atropa belladonna* root on tropine alkaloid synthesis, Master. Guizhou University, China.

Fu, Y., Xue, H., Yin, L., 2011. Application of numerical taxonomy in the morphological classification of datureae seeds. Plant Quar. 25, 47–51.

Furey, M.L., Drevets, W.C., 2006. Antidepressant efficacy of the antimuscarinic drug scopolamine: a randomized, placebo-controlled clinical trial. Arch. Gen. Psychiatry 63, 1121–1129.

Furey, M.L., Khanna, A., Hoffman, E.M., et al., 2010. Scopolamine produces larger antidepressant and antianxiety effects in women than in men. Neuropsychopharmacology 35, 2479–2488.

García Del Valle, I., Alvarez-Lorenzo, C., 2021. Atropine in topical formulations for the management of anterior and posterior segment ocular diseases. Expert Opin. Drug Deliv. 18, 1245–1260.

Gay, R., Algeo, S., Lee, R., et al., 1986. Treatment of verapamil toxicity in intact dogs. J. Clin. Investig. 77, 1805–1811.

Geeta, R., Gharaibeh, W., 2007. Historical evidence for a pre-columbian presence of *Datura* in the old world and implications for a first millennium transfer from the new world. J. Biosci. 32, 1227–1244.

Ghelardini, C., Galeotti, N., Fantetti, L., et al., 1999. Antinociceptive effect of r-(+)-hyoscyamine on the conjunctival reflex test in rabbits. Jpn. J. Pharmacol. 81, 34–37.

Ghorani-Azam, A., Sepahi, S., Riahi-Zanjani, B., et al., 2018. Plant toxins and acute medicinal plant poisoning in children: a systematic literature review. J. Res. Med. Sci. 23, 26-26.

Ghosal, S., Bang, E., Yue, W., et al., 2018. Activity-dependent brain-derived neurotrophic factor release is required for the rapid antidepressant actions of scopolamine. Biol. Psychiatry 83, 29–37.

Gil, A., Nachum, Z., Tal, D., et al., 2012. A comparison of cinnarizine and transdermal scopolamine for the prevention of seasickness in naval crew: A double-blind, randomized, crossover study. Clin. Neuropharmacol. 35, 37–39.

Godyń, J., Zaręba, P., Łażewska, D., et al., 2021. Cyanobiphenyls: Novel h3 receptor ligands with cholinesterase and mao b inhibitory activity as multitarget compounds for potential treatment of alzheimer's disease. Bioorg. Chem. 114, 105129.

Griffin, W.J., Lin, G.D., 2000. Chemotaxonomy and geographical distribution of tropane alkaloids. Phytochemistry 53, 623–637.

Grøntved, A., Brask, T., Kambskard, J., et al., 1988. Ginger root against seasickness: A conctrolled trial on the open sea. Acta Oto-Laryngol. 105, 45–49.

Guangxiao, T., Jianyao, D., Hui, P., et al., 2013. Observation on therapeutic effect of combined medicinal liquid on piglets' yellow and white dysentery. Chin. Livest. Poult. Breed. 9, 75–76.

Guihua, L., 2013. Clinical observation of scopolamine in treatment of children with persistent pneumonia. Chin. J. Clin. Rational Drug Use 6, 123.

Guirado, N., Nogueira, N.L., Ambrosano, E., et al., 2001. Vegetable extracts effect on *brevipalpus phoenicis* vector activity. Summa Phytopathol. 27, 343–347.

Hao, W., 2017. Application of atropine in acute organophosphorus insecticide poisoning. China Pract. Med. 12, 195–196.

Harfi, B., Khelifi, L., Khelifi-Slaoui, M., et al., 2018. Tropane alkaloids gc/ms analysis and low dose elicitors' effects on hyoscyamine biosynthetic pathway in hairy roots of algerian *Datura* species. Sci. Rep. 8, 17951.

Harmata, M., 2010. The (4+3)-cycloaddition reaction: Simple allylic cations as dienophiles. Chem. Commun. 46, 8886–8903.

Hasebe, F., Yuba, H., Hashimoto, T., et al., 2021. Crispr/cas9-mediated disruption of the pyrrolidine ketide synthase gene reduces the accumulation of tropane alkaloids in *atropa belladonna* hairy roots. Biosci. Biotechnol. Biochem. 85, 2404–2409.

Hayakawa, Y., Yokoyama, K., Noyori, R., 1978. Carbon-carbon bond formation promoted by transition-metal carbonyls 21. Novel cyclopentenone synthesis via iron carbonyl aided cyclocoupling between alpha,alpha'-dibromo ketones and enamines. J. Am. Chem. Soc. 100, 1799–1806.

He, Z., He, Z., Wang, J., 1999. Determination of scopolamine in flos Daturae by hplc. Chin. J. Pharm. Anal. 19, 30–32.

Hergenisa, H., 2012. To study the relationship between acute toxicity and alkaloid content of *Datura* in xinjiang. Chin. J. Ethnomed. Ethnopharmacy 21, 2–3.

Hilton, M.G., Rhodes, M.J.C., 1990. Growth and hyoscyamine production of 'hairy root' cultures of *Datura stramonium* in a modified stirred tank reactor. Appl. Microbiol. Biotechnol. 33, 132–138.

Hiraoka, N., Tashimo, K., Kinoshita, C., et al., 1996. Genotypes and alkaloid contents of *Datura metel* varieties. Biol. Pharm. Bull. 19, 1086–1089.

Holzman, R.S., 1996. The legacy of atropos, the fate who cut the thread of life. Anesthesiology 85. A952-A952.

Hong, X., Yin, M., 2010. Protective effect of ermrnwuwei - tang against acute liver injury in mice. J. Med. 16, 39–41.

Hongshun, Y., Zhifeng, W., 2016. Effect of ulinastatin combined with scopolamine on acute respiratory distress syndrome. Mod. J. Integr. Tradit. Chin. West. Med. 25, 1220-22+40.

Huang, J.-P., Fang, C., Ma, X., et al., 2019. Tropane alkaloids biosynthesis involves an unusual type iii polyketide synthase and non-enzymatic condensation. Nat. Commun. 10, 4036.

Huang, J.-P., Wang, Y.-J., Tian, T., et al., 2021. Tropane alkaloid biosynthesis: a centennial review. Nat. Prod. Rep., 38 1634–1658.

Humphrey, A.J., O'hagan, D., 2001. Tropane alkaloid biosynthesis. a century old problem unresolved. Nat. Prod. Rep. 18, 494–502.

Ibrahim, M., Siddique, S., Rehman, K., et al., 2018. Comprehensive analysis of phytochemical constituents and ethnopharmacological investigation of genus. Datura 28, 223–283.

Iida, H., Watanabe, Y., Kibayashi, C., 1985. A new synthetic route to tropane alkaloids based on 4 + 2 nitroso cyclo-addition to 1,3-cycloheptadienes. J. Org. Chem. 50, 1818–1825.

Institute, B.P.I.R., Factory, B.P., 1977. Study on the industrial synthetic method of scopolamine. Chemistry 06, 18–19.

Iqbal, S., Sivaraj, C., Gunasekaran, K., 2017. Antioxidant and anticancer activities of methanol extract of seeds of *Datura stramonium* L. Free Radic. Antioxi*dants* 7, 184–189.

Iqbal, S., Shah, F.A., Naeem, K., 2020. Succinamide derivatives ameliorate neuroinflammation and oxidative stress in scopolamine-induced neurodegeneration. Biomolecules 10, 443.

Jaafar, F.R., Ajeena, S.J., Mehdy, S.S., 2018. Anti-inflammatory impacts and analgesiac activity of aqueous extract *Datura innoxia* leaves against induced pain and inflammation in mice. J. Entomol. Zool. St*udies* 6, 1894–1899.

Javaid, A., Saddique, A., 2012. Control of charcoal rot fungus *macrophomina phaseolina* by extracts of *Datura metel*. Nat. Prod. Res. 26, 1715–1720.

Jia, L., Yao, M., Pei, G., 2018. Overview of clinical studies on chemical constituents and efficacy of *Datura*, *Journal of BingTuan*. Medicine 47–49.

Jiao, M., Luna-Cavazos, M., Bye, R., 2002. Allozyme variation in mexican species and classification of *Datura* (solanaceae). Plant Syst. Evol. 232, 155–166.

Kadir, T., 2017. Study on the change of content in *Datura stramonium* L. with different methods concocted of uyghur medicine. Guid. J. Tradit. Chin. Med. Pharm. 23, 17.

Kagale, S., Marimuthu, T., Thayumanavan, B., et al., 2004. Antimicrobial activity and induction of systemic resistance in rice by leaf extract of *Datura metel* against *rhizoctonia solani* and *xanthomonas oryzae pv. Oryzae*. Physiol. Mol. Plant Pathol. 65, 91–100.

Kamal, S., Mehrdad, K., Mahmoud, R.-K., et al., 2021. Phytotherapy for wound healing: The most important herbal plants in wound healing based on iranian ethnobotanical documents. Mini-Rev. Med. Chem. 21, 500–519.

Karim, F., Chang, P., Garrison, C., et al., 2020. Role of theophylline in management of bradycardia secondary to high cervical spinal cord injury in a seven-year-old child: Case report and a review of literature. Cureus.

Kariñho-Betancourt, E., Agrawal, A.A., Halitschke, R., et al., 2015. Phylogenetic correlations among chemical and physical plant defenses change with ontogeny. N. Phytol. 206, 796–806.

Kaushik, P., Goyal, P., 2008. In vitro evaluation of *Datura innoxia* (thorn-apple) for potential antibacterial activity. Indian J. Microbiol. 48, 353.

Kerchner, A., Farkas, Á., 2020. Worldwide poisoning potential of brugmansia and *Datura*. Forensic Toxicol. 38, 30–41.

Khan, F.Z., Alam, M., Saleem, R., et al., 1992. Biological studies of indigenous medicinal plants–i: physicochemical and antimicrobial screening of non-alkaloidal constituents of some solanaceous seeds. Pak. J. Pharm. Sci. 5, 55–61.

Khan, M.S., Tiwari, A., Khan, Z., et al., 2017. Pyridostigmine induced prolonged asystole in a patient with myasthenia gravis successfully treated with hyoscyamine. Case Rep. Cardiol. 2017.

Kim, N., Estrada, O., Chavez, B., et al., 2016. Tropane and granatane alkaloid biosynthesis: a systematic analysis. Molecules 21, 1510.

Kishore, G.K., Pande, S., 2005. Integrated applications of aqueous leaf extract of *Datura metel* and chlorothalonil improved control of late leaf spot and rust of groundnut. Australas. Plant Pathol. 34, 261–264.

Klinkenberg, I., Blokland, A., 2010. The validity of scopolamine as a pharmacological model for cognitive impairment: a review of animal behavioral studies. Neurosci. Biobehav. Rev. 34, 1307–1350.

Kohnen-Johannsen, K.L., Kayser, O., 2019. Tropane alkaloids: chemistry, pharmacology, biosynthesis and production. Molecules 24, 796.

Kossmann, C.E., 1953. The normal electrocardiogram. Circulation 8, 920–936.

Kraut, K., 1863. Ueber das atropin. Justus Liebigs Ann. der Chem. 128, 280–285.

Kumar, S., Maurya, V.K., Kabir, R., et al., 2020. Antiviral activity of belladonna during japanese encephalitis virus infection via inhibition of microglia activation and inflammation leading to neuronal cell survival. Acs Chem. Neurosci. 11, 3683–3696.

Lakstygal, A.M., Kolesnikova, T.O., Khatsko, S.L., et al., 2019. Dark classics in chemical neuroscience: atropine, scopolamine, and other anticholinergic deliriant hallucinogens. Acs Chem. Neurosci. 10, 2144–2159.

Le Garff, E., Delannoy, Y., Mesli, V., 2016. Forensic features of a fatal *Datura* poisoning case during a robbery. Forensic Sci. Int. 261, e17–e21.

Lei, J., 2011. Comparison of alkaloid content and insecticidal activity between *Datura* and its varieties, Master. Northwest Agriculture & Forestry University.

Li, B., Yan, C., Ping, X., et al., 2012. *Henosepilachna vigintioctopunctata* susceptibility to *ttripterygium wilfordii* and *Datura stramonium* extracts. Chin. J. Eco-Agric. 20, 495–500.

Li, H., Wang, X., Xia, H., et al., 2012. Callus culture of *Datura* and analysis of scopolamine. J. Liaoning Univ. (Nat. Sci.) 39, 118–122.

Li, J., Chen, M., Qiu, F., et al., 2014. Reference gene selection for gene expression studies using quantitative real-time pcr normalization in atropa belladonna. Plant Mol. Biol. Report. 32, 1002–1014.

Li, J.-D., Qin, B.-F., Yang, C.-X., et al., 2013. Enhanced biosynthesis of scopolamine in transgenic *atropa belladonna* by overexpression of *h6h* gene. Zhongguo zhongyao zazhi = China J. Chin. Mater. Med. 38, 1719–1724.

Li, N., Lee, B., Liu, R.-J., 2010. Mtor-dependent synapse formation underlies the rapid antidepressant effects of nmda antagonists. Science 329, 959–964.

Li, R., Reed, D.W., Liu, E.W., et al., 2006. Functional genomic analysis of alkaloid biosynthesis in Hyoscyamus niger reveals a cytochrome p450 involved in littorine rearrangement. Chem. Biol. 13, 513–520.

Li, S. 2016. *Compendium of materia medica* (China Medical Science and Technology Press: Beijing).

Li, X., Qiang, W., Qiu, F., et al., 2017. Cloning and characterization of an aromatic amino acid aminotransferase (arat) gene involved in tropane alkaloid biosynthesis rom Hyoscyamus niger. Acta Pharm. Sin. 52, 172–179.

Lim, S.C., Lee, M.K., Lee, C.K., et al., 2008. Evaluation of scopolamine patch pharmacotherapy for motion sickness in S. Korean. Biomol. Ther. 16, 161–167.

Lin, Y.-G., Chen, P.-H., Chang, F.-Y., et al., 2011. Delirium due to scopolamine patch in a 4-year-old boy. J. Formos. Med. Assoc. 110, 208–211.

Long, S.-P., Lu, Y., Wang, Y.-X., et al., 2013. Enhancement of tropane alkaloids production in transgenic hair roots of atropa belladonna by overexpressing endogenous genes *abpmt* and *abh6h*. Yao xue xue bao = Acta Pharm. Sin. 48, 243–249.

Lossen, W., 1864. Ueber das atropin. Justus Liebigs Ann. der Chem. 131, 43–49.

Lowe, R.A., Taylor, D., Chibale, K., et al., 2020. Synthesis and evaluation of the performance of a small molecule library based on diverse tropane-related scaffolds. Bioorg. Med. Chem. 28.

Lu, G., Li, F., 1979. Comparison of scopolamine content in corolla and calyx of *Datura metel* l. Chin. Tradit. Pat. Med. 31–33. +30.

Lu, X., Liu, Z., Huang, J., et al., 2006. Nematicidal activities and mechanisms of total alkaloids extracts from leaf of *Datura metel* Linn. Chin. Agric. Sci. Bull. 331–334.

Luna-Cavazos, M., Bye, R., Jiao, M., 2008. The origin of *Datura metel* (solanaceae): Genetic and phylogenetic evidence. Genet. Resour. Crop Evol. 56, 263.

Ma, M., Yu, F., Kong, L., 1999. Allelopathy effects of artemisia ordosica. Acta Ecol. Sin. 19, 670–676.

Manno, M., Di Renzo, G., Bianco, P., et al., 2015. Unique scopolamine withdrawal syndrome after standard transdermal use. Clin. Neuropharmacol. 38, 204–205.

Manzoor, A.M., Syed, S.H., Bashir, A.S., et al., 2019. Recent advances in metabolites from medicinal plants in cancer prevention and treatment. Curr. Immunol. Rev. (Discontin.) 15, 185–201.

Maricarmen, H.-R., Maciel, A.-M.I., Daniel, G.-M.I., et al., 2020. Chronic administration of scopolamine increased gsk3βp9, beta secretase, amyloid beta, and oxidative stress in the hippocampus of wistar rats. Mol. Neurobiol. 57, 3979–3988.

Marquart, K., Prokopchuk, O., Wilhelm, D., et al., 2019. Human small bowel as model for poisoning with organophosphorus compounds. Toxicol. Vitr. 57, 76–80.

Moeller, G., Hughes, J.J., Mangano, F.A., et al., 1992. Comparison ofl-hyoscyamine, glucagon, and placebo for air-contrast upper gastrointestinal series. Gastrointest. Radiol. 17, 195–198.

Moharrami, F., Hosseini, B., Sharafi, A., et al., 2017. Enhanced production of hyoscyamine and scopolamine from genetically transformed root culture of hyoscyamus reticulatus l. Elicited by iron oxide nanoparticles. Vitr. Cell. Dev. Biol. - Plant 53, 104–111.

Momtazi-Borojeni, A., Sadeghi-Aliabadi, H., Rabbani, M., et al., 2017. Cognitive enhancing of pineapple extract and juice in scopolamine-induced amnesia in mice. Res. Pharm. Sci. 12, 257–264.

Muthusamy, P., Nivedhitha, M., Jayshree, N., 2010. Analgesic and anti-inflammatory activities of *Datura metel* linn. Root in experimental animal models. Res. J. Pharm. Technol. 3, 897–899.

Naqvi, A.A., Mandal, S., Verma, R.K., 1998. Determination of atropine and scopolamine by proton nuclear magnetic resonance spectroscopy. Phytochem. Anal. 9, 168–170.

Nasir, B., Baig, M.W., Majid, M., et al., 2020. Preclinical anticancer studies on the ethyl acetate leaf extracts of *Datura stramonium* and *Datura inoxia*. BMC Complement. Med. Ther. 20, 188.

Nguyen, T.-K.-O., Jamali, A., Lanoue, A., et al., 2015. Unravelling the architecture and dynamics of tropane alkaloid biosynthesis pathways using metabolite correlation networks. Phytochemistry 116, 94–103.

Nocquet, P.A., Opatz, T., 2016. Total synthesis of (+/-)-scopolamine: challenges of the tropane ring. Eur. J. Org. Chem. 2016, 1156–1164.

Noyori, R., Baba, Y., Hayakawa, Y., 1974. New, general synthesis of tropane alkaloids. J. Am. Chem. Soc. 96, 3336–3338.

Osborne, D.C., Greenhalgh, K.M., Evans, M.J.E., et al., 2018. Atropine penalization versus occlusion therapies for unilateral amblyopia after the critical period of visual development: a systematic review. Ophthalmol. Ther. 7, 323–332.

Pałucha-Poniewiera, A., Podkowa, K., Lenda, T., 2017. The involvement of monoaminergic neurotransmission in the antidepressant-like action of scopolamine in the tail suspension test. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 79, 155–161.

Pan, S.Y., Han, Y.F., 2004. Comparison of the inhibitory efficacy of four belladonna drugs on gastrointestinal movement and cognitive function in food-deprived mice. Pharmacology 72, 177–183.

Parr, A.J., Payne, J., Eagles, J., et al., 1990. Variation in tropane alkaloid accumulation within the solanaceae and strategies for its exploitation. Phytochemistry 29, 2545–2550.

Payne, J., Hamill, J.D., Robins, R.J., et al., 1987. Production of hyoscyamine by 'hairy root' cultures of *Datura stramonium*. Planta Med 53, 474–478.

Ping, Y., Li, X., You, W., et al., 2019. De novo production of the plant-derived tropine and pseudotropine in yeast. ACS Synth. Biol. 8, 1257–1262.

Qiang, W., Hou, Y.-L., Li, X., et al., 2015. Cloning and expression of the key enzyme hyoscyamine 6 beta-hydroxylase gene (*dah6h*) in scopolamine biosynthesis of *Datura* arborea. Yao xue xue bao = Acta Pharm. Sin. 50, 1346–1355.

Qiao, C., Sun, H., Zhu, H., 1994. Comparative studies between *Datura metel* l.Var. Wenchowensis, a new variety of *Datura* and *d. Metel* l. Acad. J. Second Mil. Med. Univ. 549–553.

Qiu, F., 2019. Discovery and functional identification of three novel genes involved in the biosynthesis of tropane alkaloids Doctor. Southwest University.

Qiu, F., Yang, C., Yuan, L., et al., 2018. A phenylpyruvic acid reductase is required for biosynthesis of tropane alkaloids. Org. Lett. 20, 7807–7810.

Qiu, F., Zeng, J., Wang, J., et al., 2020. Functional genomics analysis reveals two novel genes required for littorine biosynthesis. N. Phytol. 225, 1906–1914.

Qiu, F., Yan, Y., Zeng, J., 2021. Biochemical and metabolic insights into hyoscyamine dehydrogenase. ACS Catal. 11, 2912–2924.

Raufman, J.-P., Shant, J., Xie, G., et al., 2011. Muscarinic receptor subtype-3 gene ablation and scopolamine butylbromide treatment attenuate small intestinal neoplasia in apc min/+ mice. Carcinogenesis 32, 1396–1402.

Renner, U.D., Oertel, R., Kirch, W., 2005. Pharmacokinetics and pharmacodynamics in clinical use of scopolamine. Ther. Drug Monit. 27, 655–665.

Repka, M.X., Kraker, R.T., Holmes, J.M., et al., 2014. A randomized trial of atropine versus patching for treatment of moderate amblyopia: Follow-up at 15 years of age. J. Am. Assoc. Pediatr. Ophthalmol. Strabismus 18, e9.

Robert, B., Rachel, M., José, P., 1991. Ethnobotany and chemistry of *Datura lanosa* (solanaceae)in mexico. Botany 61, 21–42.

Robins, R.J., Bent, E.G., Rhodes, M.J.C., 1991. Studies on the biosynthesis of tropane alkaloids by *Datura stramonium* L. Transformed root cultures. Planta 185, 385–390.

Robinson, R., 1917. Lxiii.—a synthesis of tropinone. J. Chem. Soc., Trans. 111, 762–768.

Rodriguez, S., Uria, U., Reyes, E., et al., 2021. The pseudotransannular ring opening of 1-aminocyclohept-4-ene-derived epoxides in the synthesis of tropane alkaloids: Total synthesis of (+/-)-ferrugine. Eur. J. Org. Chem. 2021, 2855–2861.

Rongzhen, L., 2012. Pharmacological effects of atropine and its clinical application in animals. China Anim. Husb. Vet. Abstr. 28, 209.

Rowson, J.M., 1944. Increased alkaloidal contents of induced polyploids of *Datura*, *Nature*, 154, 81–82.

Ruijia, S., Weizhuo, H., Jie, Y., et al., 2010. Effects of water extract from *Datura fastuosa* l. And *Chelidonium majus* l. On sterilization. J. Anhui Agric. Sci. 38, 4941–4942.

Schlesinger, D., Davidovich R., Rikanati, Faigenboim, A., et al., 2021. Tropane alkaloid biosynthesis in Datura innoxia mill. Roots and their differential transport to shoots. Phytochem. Lett. 43, 219–225.

Shakeran, Z., Keyhanfar, M., Asghari, G., et al., 2015. Improvement of atropine production by different biotic and abiotic elicitors in hairy root cultures of *Datura metel*. Turk. J. Biol. 39, 111–118.

Shang, T., 2016. Optimization of extraction technology of *Datura stramonium* l. Total alkaloids. Food Res. Dev. 37, 5.

Sharma, M., Dhaliwal, I., Rana, K., et al., 2021. Phytochemistry, pharmacology, and toxicology of *Datura* species—a review. Antioxidants 10, 1291.

Shu, B., Li, Y., 2015. Analysis of the effects of processing principle on the toxic components of *Datura white*. J. Sichuan Tradit. Chin. Med. 33, 85–87.

Silvia, G., Laura, O., Maria Concetta, R., et al., 2017. Herbal highs: Review on psychoactive effects and neuropharmacology. Curr. Neuropharmacol. 15, 750–761.

Sondhia, S., Swain, D., 2002. Allelopathic effects of *Datura stramonium* L. on rice and *echinochloa colonum*. Allelopath. J. 10, 133–140.

Spinks, A., Wasiak, J., 2011. Scopolamine (hyoscine) for preventing and treating motion sickness. Cochrane Database Syst. Rev. 32.

Srimathi, U., Nagarajan, V., Chandiramouli, R., 2018. Interaction of imuran, pentasa and hyoscyamine drugs and solvent effects on graphdiyne nanotube as a drug delivery system - a dft study. J. Mol. Liq. 265, 199–207.

Srinivasan, P., Smolke, C.D., 2020. Biosynthesis of medicinal tropane alkaloids in yeast. Nature 585, 614–619.

Stankovic, A.S., Alvarenga, D.L., Daniels, V.R.C., 2019. Intranasal scopolamine for motion sickness. Aerosp. Med. Hum. Perform. 90, 917–924.

St-Onge, M., Anseeuw, K., Cantrell, F.L., et al., 2017. Experts consensus recommendations for the management of calcium channel blocker poisoning in adults. Crit. Care Med. 45.

Strubelt, O., 1984. Antidotal treatment of the acute cardiovascular toxicity of verapamil. Acta Pharmacol. Et. Toxicol. 55, 231–237.

Sun, M., Yu, H., Guo, X., 2016. Study on plant identification and seed identification of several kinds of *Datura*. China Plant Prot. 36, 65–67.

Sun, Y., Sang, X., Yang, W., et al., 2012. Herbicidal activities of methanol extracts of 6 plants against some invasive weeds. J. Huazhong Agric. Univ. 31, 346–350.

Swathi, S., Gopal, M., Ghosh, S.K., et al., 2012. Larvicidal and repellent activities of ethanolic extract of *Datura stramonium* leaves against mosquitoes. Int. J. Pharmacogn. Phytochem. Res. 4, 25–27.

Taye, B., Giday, M., Animut, A., et al., 2011. Antibacterial activities of selected medicinal plants in traditional treatment of human wounds in ethiopia. Asian Pac. J. Trop. Biomed. 1, 370–375.

Thevan N., M., P.S.T., Manoharan, T., et al., 2005. Effect of botanicals on coconut eriophyid mite (cem), aceria guerreronis (keifer). Ann. Pl Prot. Sci. 13, 283–291.

Tran, H.D.M., Tran, Y.H., Tran, T.D., et al., 2018. A review of myopia control with atropine. J. Ocul. Pharmacol. Ther. 34, 374–379.

Tsialtas, I.T., Patelou, E., Kaloumenos, N.S., et al., 2014. In the wild hybridization of annual *Datura* species as unveiled by morphological and molecular comparisons. J. Biol. Res. 21, 1–8.

Tsialtas, J.T., Kostoglou, E., Lazari, D., 2018. Annual *Datura* accessions as source of alkaloids, oil and protein under mediterranean conditions. Ind. Crops Prod. 121, 187–194.

Ullrich, S.F., Hagels, H., Kayser, O., 2017. Scopolamine: A journey from the field to clinics. Phytochem. Rev. 16, 333–353.

Upadhyay, A., Beuerman, R.W., 2020. Biological mechanisms of atropine control of myopia. Eye Contact Lens-Sci. Clin. Pract. 46, 129–135.

Vitale, A.A., Acher, A., Pomilio, A.B., 1995. Alkaloids of *Datura* ferox from argentina. J. Ethnopharmacol. 49, 81–89.

Vlahovic, S., Schadel, N., Tussetschlager, S., et al., 2013. Tropanes as scaffolds for phosphorus-olefin ligands and their application in asymmetric catalysis. Eur. J. Org. Chem. 2013, 1580–1590.

Voleti, B., Navarria, A., Liu, R.J., et al., 2013. Scopolamine rapidly increases mammalian target of rapamycin complex 1 signaling, synaptogenesis, and antidepressant behavioral responses. Biol. Psychiatry 74, 742–749.

Wang, B., Xiao, B., Wang, H., et al. 2010. Advances in studies on the genus *Datura* (solanaceae). In The 10th Chinese Medicine Identification conference of Chinese Medicine Association and WHO Seminar on methods and Techniques of Identification of Chinese medicinal Materials, 4. Xi 'an, Shanxi, China.

Wang, B., Zuo, X., Peng, L., 2021. Melatonin ameliorates oxidative stress-mediated injuries through induction of ho-1 and restores autophagic flux in dry eye. Exp. Eye Res. 205, 108491.

Wang, H., Cheng, Y., Yu, H., 2008. Effects of extracted liquid from *Datura stramoniumon* seed germination and seedling growth of vegetables. J. Anhui Agric. Sci. 36, 15318–15320.

Wang, J. 1990. *Lu yanyan materia medica* (Beijing Buyuntang: Bei Jin).

Wang, J., Pan, K., Wu, N., 2005. Preliminary study on varietal differences in allelopathic potential of chinese prickly ash (*zanihoxylum piperitum*). Acta Ecol. Sin. 1591–1598.

Wang, K., Shi, J., Zhou, Y., 2021. Design, synthesis and evaluation of cinnamic acid hybrids as multi-target-directed agents for the treatment of alzheimer's disease. Bioorg. Chem. 112, 104879.

Wang, Q., Xiao, H., Yang, B., et al., 2008. Studies on pharmacological actions of the effective parts for psoriasis in flos *Daturae*(i) ———the anti-inflammatory, anti-titillation and anti-anaphylaxis actions of flos *Daturae*. Chin. J. Exp. Tradit. Med. Formula 49–51.

Wang, X., Zhang, F., Feng, T., et al., 2009. Study on the antibacterial activity of the alkaloid extracts from the seeds of *Datura*, *Gansu*. Agriculture 90–92.

Wang, X., Chen, M., Yang, C., et al., 2011. Enhancing the scopolamine production in transgenic plants of *atropa belladonna* by overexpressing pmt and h6h genes. Physiol. Plant. 143, 309–315.

Wang, Y., 2014. *Datura* can numb people. Juv. Sci. 32–33.

Wei, S., Fu, Y., Xue, H., 2011. Taxonomic study of *Datura*: Inferences from its sequences of nuclear ribosomal. DNA, Plant Quar. 25, 12–16.
Weijun, Y., 2015. Observation on the curative effect of scopolamine combined with dexamethasone in the treatment of acute toxic pulmonary edema. J. Clin. Pulm. Med. 20, 358–360.
Wigenstam, E., Forsberg, E., Bucht, A., et al., 2021. Efficacy of atropine and scopolamine on airway contractions following exposure to the nerve agent vx. Toxicol. Appl. Pharmacol. 419, 115512.
Willstätter, R., 1901. Synthesen in der tropingruppe. I. Synthese des tropilidens. Justus Liebigs Ann. der Chem. 317, 204–265.
Win Ning, C., Keng Yoon, Y., 2020. Scopolamine, a toxin-induced experimental model, used for research in alzheimer's disease. CNS Neurol. Disord. - Drug Targets 19, 85–93.
Xia, K., Liu, X., Zhang, Q., 2016. Promoting scopolamine biosynthesis in transgenic *atropa belladonna* plants with *pmt* and *h6h* overexpression under field conditions. Plant Physiol. Biochem. 106, 46–53.
Xiang, X.-H., Wang, H.-L., Wu, W.-R., et al., 2006. Ethological analysis of scopolamine treatment or pretreatment in morphine dependent rats. Physiol. Behav. 88, 183–190.
Xiaoping, W., 2012. Application of atropine. China Pract. Med. 7, 157–158.
Xiufen, Y., and Guangwen, L. 2001. Study on the eects of semio-chemical of plant on the oviposition deterrent of tobacco whitefly (*Bemisia tabaci* genn). In *Insects and Environment-Proceedings of the 2001 Annual Conference of the Chinese Entomological Society*, 6. Chengdu, Sichuan, China.
Xu, L., Zhou, T., 1965. Amperometric titration of alkaloids. Determination of total alkaloids in *belladonna* and *Datura*. Acta Pharm. Sin. A 388–391.
Xu, S., Zhai, J., Xu, K., et al., 2021. M1 macrophages-derived exosomes mir-34c-5p regulates interstitial cells of cajal through targeting scf. J. Biosci. 46, 90.
Xue, P., Chen, Y., Qing, M., et al., 2011. Determination of scopolamine in mongolian medicine *Datura* by hplc. Chin. J. Hosp. Pharm. 28, 164–167.
Yadav, H., Yadav, M., Jain, S., et al., 2008. Antimicrobial property of a herbal preparation containing *Dalbergia sissoo* and *Datura stramonium* with cow urine against pathogenic bacteria. Int. J. Immunopathol. Pharmacol. 21, 1013–1020.
Yamada, Y., Tabata, M., 1997. Plant biotechnology of tropane alkaloids. Plant Biotechnol. 14, 1–10.
Yan, Z., Pan, X., Qiang, W., et al., 2014. Improvment of biosynthesis of transpane alkaloids in anisodus acutangulus by co-transformed pmt and h6h. J. Southwest Univ. (Nat. Sci. Ed.) 36, 21–27.
Yang, J., Zhang, Z., Ye, T., 2019. Effects of different parts of *Datura stramonium* on the *Solenopsis invicta* buren workers. J. South. Agriculture 50, 2475–2480.
Yu, L., Yang, D., Hu, S., 1992. Determination of scopolamine in *Datura metel* L. by reversed-phase high performance liquid chromatography. Chin. Tradit. Pat. Med. 14, 35–36.
Zhang, H., Tang, S., 1958. Observation on the change of total alkaloid content in five kinds of *Datura* during cultivation. Acta Pharm. Sin. A 107–111.
Zhang, H., Han, C., Cheng, M., 2007. Study on killing mouse of 30. Plants, Acta Bot. Boreal. -Occident. Sin. 2545–2550.
Zhang, L., Ding, R., Chai, Y., et al., 2004. Engineering tropane biosynthetic pathway in *Hyoscyamus niger* hairy root cultures. Proc. Natl. Acad. Sci. USA 101, 6786.
Zhang, M., Jin, D., Lv, L., 2006. The drive action of extracts from *Datura stramonium* and *Metaplexis japonica* to *tetranychus truncatus*. J. Agric. Sci. Yanbian Univ. 52–55.
Zhang, Q., Wang, C., Ma, X., 2021. Determination of scopolamine in *Datura* medicinal wine by gas chromatography-mass spectrometry. China Food Saf. Mag. 62–63.
Zhang, Q., Liang, M., Zeng, J., et al., 2022. Engineering tropane alkaloid production and glyphosate resistance by overexpressing *abcam1* and *g2-epsps* in *atropa belladonna*. Metab. Eng. 72, 237–246.
Zhang, X., Zhang, H., Shi, X., 2015. Distribution of scopolamine and scopolamine in *Datura* from guizhou. Chin. Med. Mater. 38, 49–52.
Zhao, Y., 2011. Comparative Study on Morphological Diversity and Alkaloid Content in Different Populations of *Datura* (Master). Northwest Agriculture & Forestry University.
Zheng, D., 1980. Experimental study on traditional chinese medicine anesthesia of cattle (second report) determination of several kinds of *Datura* and observation of its anesthetic effect. Chin. J. Tradit. Vet. Sci. 60–64.
Zheng, X., Li, C., 2008. Effects of *Datura stramonium* L.'s alkaloids on maize seeds germination and seedling growth. J. Southwest China Norm. Univ. (Nat. Sci. Ed.) 121–125.
Zheng, X., Li, C., Lu, H., et al., 2007. Influence of alkaloid extracts from *Datura stramonium* L. on germination of several plant seeds. Seed 38–40.
Zhou, J., Hu, G., Liu, M., et al., 2008. Contact and antifeeding effects on four species of the genus *Datura* against *mythimna separate* and *Pieris rapae*. J. Gansu Agric. Univ. 43, 102–106.
Zhou, L., Sun, S., Wu, Z., et al., 2009. Study on the herbicidal activity of *Datura stramonium* L. Henan Agric. Sci. 91–94.
Zhou, L., Huang, J., Sun, Y., 2011. Herbicidal activities of methanol extracts of 29 plants against *Pistia stratiotes* L. J. Huazhong Agric. Univ. 30, 200–205.
Zhu, H., Feng, R., Hu, L., 2015. Preliminary antifungal research of *Datura stramonium* on phytopathogens. J. Henan Inst. Sci. Technol. 43, 30–32.
Zhu, X., 1998. Three kinds of ancient books of lingnan materia medica. China Traditional Chinese Medicine Science and Technology Press, Beijing.