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Pharmacological and toxicological effects of *Nicotiana tabacum*

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Abstract

Nicotiana tabacum (Family: Solanaceae) was used traditionally for wide range of disorders, it administered externally for bites of poisonous reptiles and insects, pain, neuralgia, gout, to enhance hair growth, in the treatment of ringworm, ulcers, wounds and as respiratory stimulant. The leaves contained sesquiterpene, alkaloids, lignans, flavonoids, phenolic compounds, tannins, steroids, terpenoids, cardiac glycosides, essential oils, saponins, quinines, polypeptides, phenylpropanoids, chromanones, biphenyls and isocoumarins. The previous studied showed that *Nicotiana tabacum* possessed many pharmacological effects included antioxidant, antimicrobial, antiparasitic, analgesic, antidiabetic, antifertility, anti-aphthous, cytotoxic and neuropharmacological effects. The current review focused on the chemical constituents and pharmacological effects of *Nicotiana tabacum.*

Keywords: Constituents; Pharmacology; Toxicology; *Nicotiana tabacum*; Tobacco

1. Introduction

In the last few decades there has been an exponential growth in the field of herbal medicine. Plants generally produce many secondary metabolites which are bio-synthetically derived from primary metabolites and constitute an important source of chemicals which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours and biopesticides(1-13). *Nicotiana tabacum* (Family: Solanaceae)was used traditionally for wide range of disorders, it administered externally for bites of poisonous reptiles and insects, pain, neuralgia, gout, to enhance hair growth, in the treatment of ringworm, ulcers, wounds and as respiratory stimulant. The leaves contained sesquiterpene, alkaloids, lignans, flavonoids, phenolic compounds, tannins, steroids, terpenoids, cardiac glycosides, essential oils, saponins, quinines, polypeptides, phenylpropanoids, chromanones, biphenyls and isocoumarins. The previous studied showed that *Nicotiana tabacum* possessed many pharmacological effects included antioxidant, antimicrobial, antiparasitic, analgesic, antidiabetic, antifertility, anti-aphthous, cytotoxic and neuropharmacological effects. The current review was designed to highlightthe chemical constituents and pharmacological effects of *Nicotiana tabacum*.

2. Plant profile

2.1. Synonyms

Nicotiana alba, Nicotiana capensis, Nicotiana caudate, Nicotiana chinensis, Nicotiana crispula, Nicotiana florida, Nicotiana frutescens, Nicotiana gigantean, Nicotiana gracilipes, Nicotiana guatemalensis, Nicotiana havanensis, Nicotiana lancifolia, Nicotia nalatissima, Nicotiana lehmannii, Nicotiana lingua, Nicotiana macrophylla, Nicotiana marylandica, Nicotiana mexicana, Nicotiana mexicana var. rubriflora, Nicotiana pallescens, Nicotiana pilosa, Nicotiana serotina, Nicotiana tabaca, Nicotiana verdon, Nicotiana ybarrensis, Tabacum latissimum, Tabacu mnicotianum and *Tabacum ovatofolium*[14].

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2.2. Taxonomic classification

- Kingdom: Plantae
- Subkingdom: Viridiplantae
- Infrakingdom: Streptophyta
- Superdivision: Embryophyta
- Division: Tracheophyta
- Subdivision: Spermatophytina
- Class: Magnoliopsida
- Superorder: Asteranae
- Order: Solanales
- Family: Solanaceae
- Genus: Nicotiana
- Species: *Nicotiana tabacum*[15].

2.3. Common names

- Arabic: Tobgh, Totan, Skair, Tabaaq, Tanbak, Tanbako
- Chinese: yancao
- English: tobacco
- French: tabac, tabaccommun
- German: Tabak, virginischer Tabak
- Hindi: Bajr-bhang, Tambaku, Tumak
- Italian: tobacco;
- Japanese: Nikochianatabakamu, Tabako
- Korean: dambae;
- Persian: Bajr bhang, Tanbaku, Tutun, Tutuni Kurdistan
- Spanish: tabaco
- Swedish: virginiatobak
- Turkish: Tutun[16].

2.4. Distribution

Almost all species of tobaccowas originated in South America and now cultivated worldwide as a cash crop [17].

2.5. Description

Herbs viscid, annual or short-lived perennial, 0.7-2 m tall. Leaves cauline, 24-40 x 13-25 cm, oblong to broadly elliptic-ovate, cuneate or ± auricled, texture thin. Flowers pink, in axillary and terminal compact corymboid panicles. Calyx 10-12 mm long, oblong, persistent in fruit; lobes unequal. Corolla tube 3.5-4.6 cm long, glandular-hairy without; limb up to 15 cm broad, lobes acute to apiculate. Anthers 3 mm long, oblong; filaments ± 3.5 cm long. Capsule 20 mm long, oblong-ovoid. Seeds less than 1 mm long, angled, minutely ruminate, brown [18, 19].

2.6. Traditional uses

The written history of tobacco started in the year 1492 when Christopher Columbus discovered American Indians treating patients with leaves of (*Nicotiana tabacum*) a herb which he had never seen before. In 1536, European travelers to the New World carried home a considerable medical knowledge concerning the plant, acquired from Native American. Then the Western European physicians adopted tobacco as medicine [20,21].Tobacco plant was used mainly as an ingredient of cigarettes, cigars and chew. Tobacco has long been removed from pharmacopoeias and from medical practice. However, tobacco traditionally used for wide range of disorders, itadministered externally for bites of poisonous reptiles and insects, pain, neuralgia, gout, to enhance hair growth, in the treatment of ringworm, ulcers, wounds and as respiratory stimulant. It was administered by rectum in constipation and haemorrhoidal bleeding, administered orally in strangulated hernia, malaria or intermittent fever, dislodging obstructive material from esophagus by inducing vomiting, and it administered by inhalation in nasal polyps [22-24].

An ointment made of burned tobacco leaves mixed with lanolin was used as dessicant, stimulant and antiseptic for pruritus, ringworm, athlete's foot, superficial ulcers and wounds [23].

2.7. Parts used

Leaves, stem and nicotine isolated from the plant were used medicinally [25].

2.8. Physicochemical characteristics

The physicochemical properties of *Nicotiana tabacum* stem were: total ash 1.06±0.07-3.33±0.098%, water soluble ash 11.1±0.06-15.9±0.21%,acid insoluble ash 10.28± 0.014- 16.21±0.12%, foreign organic matter 0.48±0.06-2.44±0.41%, extractive value: petroleum ether 0.48±0.052-1.13±0.05%, chloroform 0.35±0.05-0.77±0.03%,ethanol 9.68±0.07-13.45±0.10% and water 8.73±0.16-15.90±0.09%[26].

2.9. Chemical constituents

The preliminary phytochemical analysis showed that *Nicotiana tabacum* leaves contained sesquiterpene, alkaloids, lignans, flavonoids, phenolic compounds, tannins, steroids, terpenoids, cardiac glycosides, essential oils, saponins, quinines, polypeptides, phenylpropanoids, chromanones, biphenylsand isocoumarins[27-28].

Phytochemical screening of stem extracts of *Nicotiana tabacum*,showed that the stem contained alkaloids, carbohydrates, saponins, phenols, flavonoids, tannins, phytosterols and triterpenes [26].

Nicotiana tabaccum leaf contained many alkaloids includednicotine (4.19%), nicoteine, nicotyrine, nicotimine, nicotelline, isonicoteine, nornicotine, anabaine, anatalline, anabasine, anatabine and myosmine[29, 30].

Many sesquiterpenes included nicotiana sesterpenes A and B, tabasesquiterpenes A–C, glutinosone, capsidiol, 1-bhydroxy-a-cyperone,arundinol B, 3-hydroxy solavetivone-beta-D-glucoside A and Band14-noreudesmane sesquiterpenes were isolated from *Nicotiana tabacum* leaves [28,31-35].

The total flavonoids contents of tobacco leaves were 10.83 ± 0.91 mg rutin equivalent/g dry weight and the polysaccharides contents were 49.82 ± 3.42 mg/g dry weight (46.61 ± 3.11 mg/g neutral polysaccharide and 3.21 ± 0.22 mg/g acidic polysaccharides). The total phenolic contents of the flavonoid and polysaccharidic fractions were 23.2 ± 1.31 and 0.74 ± 0.04 mg galic acid equivalent /g, respectively.

However, the total flavonoid and phenolic content in the ethanolic extract of stem of *Nicotiana tabacum* were 12.5±0.1322 mg QE/ g of extract and 1133.25 ±0.02 mg QE/g, respectively [36-37]. The dominant polyphenols in tobacco leaf were identified as chlorogenic acid and rutin[38].

However, *Nicotiana tabacum* cv. Xanthiwas sensitive to tobacco mosaic virus infection, mosaic virus infection leads to the production and accumulation of a great number of phenolics, coumarins and flavonols. Phenolic acids accumulated with the infection included: quinic esters(3- caffeoylquinic acid (chlorogenic acid), 4-caffeoylquinic acid, 5-caffeoylquinic acid, 3-feruloylquinic acid, 4-feruloylquinic acid, 5-feruloylquinic acid, 3-p-coumaroylquinic acid); glucose esters (1-caffeoylglucose, 1-ferulo ylglucose, 1-o-coumaroylgentiobiose (neochlorogenic acid), lucose esters l-o-coumaroylglucose, melilotoside (o-coumaric acid glucoside), melilotic acid glucoside); glycosides (vanillic acid glucoside, p-hydroxybenzoic acid glucoside, gentisic acid glucoside). The identified coumarins were: (scopolin (scopoletin 7-glucoside), cichoriin (esculetin 7-glucoside), scopoletin 7-gentiobioside). While, the recorded flavonols were (rutin (quercetin 3-rutinoside), nicotiflorin (kaempferol 3-rutinoside), isoquercitrin (quercetin 3-glucoside), quercetin-3,3-dimethyl ether and quercetin-3- methyl ether)[21,39].

Thirty six compounds were isolated from the essential oil of the fresh leaves of *Nicotiana tabacum*. These included cyclohexane8.43%, p-xylene 12.37%, 3-methyl-octane0.88%, 1-ethyl-3-methylcyclohexane 2.59%, nonane 4.35%, 3, 5-dimethyl-3-heptene1.44%,(1-methylethyl) - cyclohexane1.70%, propyl-cyclohexane2.20%, 2, 6-dimethyl-octane1.04%, propyl- benzene, 1.64%, 1-ethyl-3-methyl- benzene2.19%, 1, 3-dimethyl-2- cyclopentane0.99%, octahydro-2, 5-dimethyl-pentalene1.80%, 1, 2, 3-trimethyl- benzene8.73%, 1-methyl-2-propyl-cyclohexane0.52%, decane3.60%, 1, 2, 5-trimethyl- benzene2.10%, 4-methyl-decane1.02%, buthyl-cyclohexane0.76%, decahydro-naphthalene, 1.05%, 1-methyl-2-(1-methylethyl)- benzene1.45%, E-2-tetradecaen-1-ol1.00%, 1-ethyl-2, 4-dimethyl-benzene0.80%, undecane2.49%, 6, 8-nonadien-2-one2.63%, isocaryophillene0.54%, 2, 6-dimethyl-heptadecane0.52%, tridecanal0.99%, 3, 7, 11, 15-tetramethyl-2-hexadecen-1-ol16.37%, thunbergol1.78%, 9-dodecyltradecahydro-anthracene0.73%, farnesol3.08%, 1-naphthalenepropanol3.08%, docosane1.34% and 9-methyl- nonadecane2.97%[40].

The seeds of *Nicotiana tabacum* contained 41.3% lipids. The lipid class of the seeds of *Nicotiana tabacum* were hydrocarbons (1.4%), wax esters (1.7%) sterol esters (2.4%), triacylglycerols (69.3%), free fatty acids (6.2%), l,3-

diacylglycerols (4.6%), l,2-diacylglycerols (3.5%), free sterols (2.3%), 2-monoacylglycerols (2.1%), 1-monoacylglycerols (1.8%), phosphatidyl ethanolamines (1.7%), phosphatidyl cholines (0.9%), lysophosphatidyl ethanolamines (1.5%) and phosphatidyl inositols (0.6%)[41].

However, chemical analysis of the seed, showed that they contained cycloartanol, cycloartenol 24-daturadiol and solavetivone. Cholesterol, cholest-7- enol, 24-methylenecholesterol, campesterol, stigmasterol, sitosterol, 28-isofucosterol, lanosterol, 31- norlanosterol, lanost-8-enol, obtusifoliol, 31-norcycloartenol, cycloeucalenol, granisterol, citrostadienol, β-amyrin, lupeol, cycloartanol and 24- methylene cycloartanol, Palmitic, oleic and linoleic acids were identified in seed oil[42, 43].

2.10. Pharmacological effects

2.10.1. Antioxidant effect

The antioxidant properties of flavonoids and polysaccharides of *Nicotiana tabacum* leaves were evaluated using DPPH, ABTS and reducing power tests. Tobacco leaves flavonoids possessed comparable superoxide anion, DPPH and ABTS radical scavenging abilities to ascorbic acid at high concentration (600 μg/ml). Furthermore, it was found that flavonoids possessed prominent effects on the reducing power, equivalent to ascorbic acid, and was significantly higher than polysaccharides [37].

The antioxidant activity of extracts of the stem of *Nicotiana tabacum* was studied by estimation ofthe superoxide dismutase, catalase, glutathione content, glutathione S transferase and lipid peroxidase. Methanolic extract showed high antioxidant activity [44].

The antioxidant activities of polyphenols from tobacco leaf were confirmed, by DPPH free radical scavenging (IC_{50}: 5.02 μg/ml), hydroxyl radicals (IC_{50}: 49.6 μg/ml) and superoxide anion radicals (IC_{50}: 44.0 μg/ml) and inhibition activity of lipid peroxidation (IC_{50}: 132 μg/ml)[38].

The antioxidant activity of polyphenolic flavonoids in the ethanolic extract of stem of *Nicotiana tabacum* was studied using DPPH free radical scavenging, enzymatic biochemical assay (SOD and GST activity) and nonenzymatic biochemical assay (GSH content and lipid peroxidation). The extract possessed antioxidant activity, flavonoid and phenolic content were 12.5±0.1322 mg QE/ g and 1133.25±0.02 mg QE/g of extract respectively, and ethanolic extract showed the highest level of SOD, GST, GSH and MDA content [36].

2.10.2. Antimicrobial effects

The antimicrobial activities of *Nicotiana tabacum* extracts were studied against human pathogens, clinical bacterial isolates, and biofilm forming bacteria. The inhibitory spectra of the extracts against the human strains ranged between 66.29±11.61 mm^2 and 159.9 ±11.31 mm^2. The highest inhibitory value of 159.9±11.31 mm^2 was recorded against *Staphylococcus aureus* followed by 119.23 ± 18.7mm^2 against *Pseudomonas aeruginosa*, and 66.29 ± 11.61mm^2against *K. pneumonia*. Against the clinical isolates, the highest inhibitory value of 97.41 ± 19.62 mm^2 was noted against *S. aureus*, while, the Gram negative pathogen, *Salmonella enteric* subsp. *enteric* serotype Typhi (72.8 ± 12.9 mm^2) was found to be quite resistant. Regarding the tested biofilm forming uropathogens, the inhibitory area was 130.72 ± 12.5 and 147.5 ± 10.82 mm^2 against *E. coli* and *Klebsiella* species respectively [17].

The bacterial growth inhibitory effect of polyphenols from tobacco leaf was studied against*Escherichia coli*, *Staphylococcus aureus* and *Bacillus subtilis*. Polyphenols possessed antibacterial effects and diameters of inhibition zones of 20.23 ± 0.42, 17.66 ± 0.86 and 12.89 ± 0.29 mm, respectively [38].

The antimicrobial activity of methanol and water extracts of the leaf and ground snuff of *Nicotiana tabacum* was investigated against *Candida albicans* and *Streptococcus pyogenes*. Methanol extracts of tobacco leaf produced zones of inhibition of 13.0 mm against *Streptococcus pyogenes* and 9.5 mm against *Candida albicans*, while, the water extracts produced inhibition zone of 10.0 mm against *Streptococcus pyogenes* with no inhibitory activity against *Candida*. MIC of the methanol extracts of tobacco leaves was 25 mg/ml against *Candida albicans* and 100 mg/mlagainst *Streptococcus pyogenes*. The zones of inhibition obtained for methanolic extracts of grounded snuff against *Streptococcus pyogenes* was 10.5 mm and against *Candida albicans* 15.0 mm, while, the water extracts produced inhibition zones of 7.5 mm a*gainst Streptococcus pyogenes* and 11.0 mm against *Candida albicans*. MIC of 100 mg/ml was recorded by both methanolic and water snuff extracts against *Streptococcus pyogenes* [45].

Antibacterial activity of extracts of the stem of *Nicotiana tabacum* was studied against two Gram positive bacteria (*Bacillus amyloiquefaciens* and *Staphylococcus aureus*) and two Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*). The methanolic and ethanolic extracts possessed maximum antibacterial activity against *Staphylococcus aureus* with diameter of inhibition of 10.667±1.527 mm and 8±1.00 mm, respectively. Methanolic extract also showed moderate inhibitory effect against *Pseudomonas aeruginosa* with an inhibitory diameter of 5.33±1.154 mm, while, ethanolic extract possessed antibacterial activity against *Bacillus amyloliquefaciens* with an inhibition diameter of 4.667±1.154 mm [44].

The ethanolic heat reflux extract (20, 40, 60, 80 and 100 %.) of *Nicotiana tabacum* var. *virginia* was tested for antibacterial activity against nosocomial bacteria pathogen ((*Pseudomonas aeruginosa* (ATCC 27853), *Eschericia coli* (ATCC 25922), *Staphylococcus aureus* (ATCC 25923), *Enterococcus faecalis* (ATCC 29212)). The highest inhibitory effects were recorded in 100% concentration against both *Staphylococcus aureus* and *Enterococcus faecalis*[46].

The antibacterial activity of extracts of *Nicotiana tabacum* at different concentrations (6, 12, 18 and 24 mg/disc)in different polar solvents (ethanol, ethyl acetate, n-hexane, acetone, butanol and water) was studied against seven pathogenic bacteria. The result revealed that ethyl acetate extracted samples were more effective against *Bacillus cereus* and *Erwinia carotovora* followed by butanol extracted samples against *Staphlococcus aureus* and *Agrobacterium tumefaciens*, while no significant inhibitory effects were observed in ethanol and hexane extracts[47].

The effect of tobacco leaves extract as an anti-biofilm agent was studied against *Staphylococcus aureus*, which was the leading cause of biofilm formation in medical equipment and implantable devices. Tobacco leaves pyrolysis extract in 20%, 40%, 60%, 80%, and 100% didn't inhibit the biofilm formation [48].

Nicotine was complexed with zinc and tested for antibacterial activity against ten different strains of Gram positive and Gram negative bacteria. The results showed that nicotine and zinc complex was more effective against different types of bacteria compared to zinc metal salt, and nicotine alone [49].

Several nicotinic and isoniazid derivatives, showedanti-mycobacterium effect when tested *in vitro* compared with first line drugs such as isoniazid and rifampicin [50].

However, *Mycobacterium tuberculosis* isolated from tuberculosis patient sputum resisted both water and ethanolic extracts of *Nicotiana tobacum*[51].

A novel pathogen- and wound-inducible protein of 20 kD was purified from tobacco (*Nicotiana tabacum*) leaves exhibited antifungal activity against *Trichoderma viride* and *Fusarium solani* by causing lysis of the germ tubes and/or growth inhibition [52].

Nicotiana tabacum leaves extract macerated in cow urine for 28 days, showed promising effect against *Malassezia furfur*, inducing a zone of inhibition of about 7 mm at 100 mg/ml and26 mm at 500 mg /ml [53].

Many sesquiterpenes isolated from *Nicotiana tabacum* exhibited high anti-tobacco mosaic virus (anti-TMV) [28-29,33-34].

2.10.3. Antiparasitic effect

The antiparasitic effect of crude aqueous methanol *Nicotiana tabacum* leaves extract was evaluated against oxfendazole-resistant *Haemonchus contortus* in sheep by using hatch assay, adult motility test and fecal egg count reduction test. The extract caused dose and time dependent nematicidal activity with LC_{50} values of 0.566 and 1.91 mg/ml in egg hatch assay and adult motility test, respectively. There was, however, no significant difference ($P>0.05$) in fecal egg count reduction (87.5 vs 88.6%) in sheep at low (2g/kg bw) and high (4g/kg bw) doses. Administration of *Nicotiana tabacum* leaves extract at low dose (2 g/kg bw) did not exhibit side effects in animals [54].

The anthelmintic activity of *Nicotiana tabacum* leaves extracts (crude aqueous and methanol extract)was studied using *in vitro* and *in vivo* models. Both the extracts causedparalysis and/or mortality of worms noted at 6 h post-exposure *in vitro*. In *in vivo* study, both extracts were administered in increasing doses (1.0-3.0 g/kg) to sheep naturally infected with mixed species of gastrointestinal nematodes. A maximum reduction of 73.6% in eggs per gram of faeces was recorded on day 5 post-treatment with crude methanolic extract (3.0 g/kg) while the same dose of crude aqueous extract showed a 49.4% reduction [55].

The *in vitro* anthelminthic effect of aqueous and alcoholic extract (25, 50 and 75 mg/ml) of *Nicotiana tabacum* was studied against *Marshallagiamarshalli* compared with levamisole.The aqueous extract at 25 and 50 mg/mldilution possessedthe same anthelminthic effects ($P<0.05$), but 75 mg/ml of the aqueous extract and 25, 50 and 75 mg/ml of alcoholic extract possessed more anthelminthic effect ($P<0.05$) [56].

The ovicidal, adulticidal effects of *Nicotiana tabacum* leaf extract, garlic (*Allium sativum*) bulb extract, soft soap and their binary mixtures were investigated against *Tetranychus urticae*. The results showed that the tobacco leaf extract, the soft soap and the garlic extract soap mixture were the most toxic against adult females. Although the garlic bulb extract had the lowest toxic effect, its mixtures with the soft soap and tobacco extract showed higher toxicity against the adults. Furthermore, the tobacco application at the tested dose significantly reduced the *T. urticae* fecundity [57].

The acaricidal activity ofacetone and aqueous extracts of the leaves of*Nicotiana tabacum* and deltamethrin were tested against *Rhipicephalus* (*Boophilus*) *microplus* fresh larvae using larval packet test. The LC_{50} and LC_{99} were highest for aqueous leaf extract at 728.97 and 6094.438 ppm, respectively [58].

A mosquito repellent paints was formulated from the extract of tobacco leaves. The results showed that 5% concentration of tobacco extract killed half of the mosquito population in 2 hours, the concentration of tobacco extract between 3-5% killed half the mosquito population in 4 hours, while 1-3% and 0-1% concentration of tobacco extract killed half the mosquito population during 6 and 24 hours, respectively [59].

The effect of leaf and seed extract of *Nicotiana tabacum* in the management of larvae, pupae and adults of *Anopheles gambiae* was assessed at five different concentrations (0.1%, 0.2%, 0.3%,0.4% and 0.5%) at ambient temperature (28±2 ^{0}C) and relative humidity (75±5%). Both extracts of *Nicotiana tabacum* elicited 100% mortality in larvae, pupae and adults of *An. gambiae* at the highest concentration. LC_{50} values revealed that leaf extract showed more toxicity than the seed extract. The LC_{50} values of leaf and seed extract of *Nicotiana tabacum* also increased with the developmental stages of the mosquitoes with the lowest and highest observed in larval (leaf: 0.153µg/ml; seed: 0.188µg/ml) and adult (leaf: 0.219 µg/ml; seed: 0.290 µg/ml) stage respectively. Median LC_{50} values were recorded in pupae of *An. gambiae* (leaf: 0.176 µg/ml; seed: 0.213µg/ml)[60].

The crude methanolic leaf extract of *Nicotiana tabacum* was evaluated for larvicidal activity against *Aedes aegypti* at concentrations of 62.5, 125, 250, 500 and 1000 ppm. *Nicotiana tabacum* exhibited high larvicidal activity with LC_{50} values of 313.58 and 122.99 ppm respectively after 24 and 48 hours [61].

The larvicidal effect of *Nicotiana tabaccum* leaves extracts was investigated against the larvae of *Anopheles* and *Culex* mosquitoes. Tobacco leaf extract caused100% mortality rate at 80 and 100% concentrations [62].

The effectiveness of tobacco extract nanoemulsion was studied against *Aedes aegypti*larvae. Bioassay of larvicidal nanoemulsion revealed that the decrease in LC_{50} values was directly proportional to the decrease in particle size. The lowest LC_{50} values were obtained by the average particle size of 631 nm. The larvicidal activity of tobacco was attributed to its nicotine and some toxic content [63].

Bio-oil extracted from tobacco leaves using fast pyrolysis at temperature of 500, 600, and 700^{o}C wasmade into bio-mass based repellent. The repellent efficacy was 38.09%; 45.82%; 46.41% and 57.07%, respectively, at concentrations of (0%, 0.5%; 1.5% and 3%). The active compounds of repellency were nicotine, d-limonene, indole, and pyridine [64-65].

The crude 95% ethanol extracts of tobacco leaves containing nicotine as an active ingredient was tested as pesticide. The emulsion formulation was studied against aphids (*Aphis glycines* Mats.) in the experiment field. It killed all of the aphids [66].

2.10.4. Analgesic effects

The analgesic activities of the methanolic leaf extract (100, 200 and 300mg/kg bw, orally) of *Nicotiana tabacum* was evaluated using tail immersion and hot plate and acetic acid- induced abdominal constrictions or writhing in mice. *Nicotiana tabacum* extracts exhibited good level of analgesic effect, it significantly increased the pain reaction time or latency period in the mice in a dose dependent manner [21, 67].

The methanolic extract of the leaves of *Nicotiana tabacum* and significantly decreased the mean total number of abdominal constrictions or writhes in a dose dependent manner, the percentage protection of the abdominal constriction reflex was also increased at a dose of 300mg/kg of the extract. Methanolic leaf extract of *Nicotiana tabacum*

showed significant analgesic effect, which could be attributed to both central and peripheral nociceptive mechanisms [68].

2.10.5. Antidiabetic effect

The hypoglycemic activities of hydroethanolic leaf extract of *Nicotiana tabacum* was evaluated using oral glucose tolerance test and normoglycemic rats. The single-dose study showed that 40 and 80mg/kg bw of the extract significantly ($P<0.05$) reduced blood glucose levels at 2h compared to control (27.35% and 28.37% at 6h compared to control 75.40%). The oral glucose tolerance test also showed that the extract caused significant reduction ($P<0.05$) in blood glucose levels [69].

2.10.6. Antifertility effect

The aqueous extract of *Nicotiana tabacum* (20 and 30mg/kg) administered for a period of 21 days in rats caused significant decrease in sperm motility and concentration and decreased spermatogenic cells in the histological sections of the testis[70].

2.10.7. Anti-aphthous activity

A randomized double-blinded placebo-controlled clinical trial was performed to determine the effects of *Nicotiana tabacum*leaves decoction as a mouthwash on minor recurrent aphthous. In the treatment group, ulcer pain score was decreased by 79.2% and 93.8% and ulcer size was reduced by 69.1% and 92.2% (at days 3 and 5, respectively), significantly greater than the control group ($P< 0.01$). No minor and major adverse effects were observed [71].

2.10.8. Cytotoxic effect

A sesquiterpene (tabsesquiterpene A) isolated from the leaves of *Nicotiana tabacum* was tested for cytotoxic activity against five cell lines(NB4, A549, SHSY5Y, PC3 and MCF7) using the MTT method. The isolated compound exhibited modest cytotoxicity against SHSY5Y, PC3 and MCF7 with IC_{50} values of 6.9, 4.5 and 8.8 μM, respectively [35].

3. Neuropharmacology of nicotine

Nicotine from tobacco induced stimulation and pleasure, and reduced stress and anxiety in human. Smoking improved concentration, reaction time, and performance of certain tasks. With higher doses, nicotine caused tremors leading to convulsions at toxic doses. The excitation of respiration was a prominent action of nicotine. Nicotine induced vomiting by both central and peripheral actions. When a person stopped smoking, nicotine withdrawal symptoms will emerged. These include irritability, depressed mood, restlessness, anxiety, difficulty concentrating, hunger, insomnia, and craving for tobacco. If untreated, smokers developed mood disturbances [21,72-73].

Nicotiana tabacum extract show anti-Alzheimer's activity and improved memory [74]. (3H) acetylcholine and (3H) nicotine were used to label nicotinic cholinergic binding sites in cerebral cortical tissues obtained at autopsy from patients with Alzheimer's disease and from matched controls. A consistent and severe loss of nicotinic receptors was found in Alzheimer's disease [75].

Rats with lesion associated with neurochemical and cellular changes resembling those seen in human Alzheimer's disease, were treated with nicotine (0.1, 0.2, 0.4 mg/kg). Treated rats showed an enhanced locomotor response after injections of nicotine compared with sham operated or un-operated controls [76].A double-blind placebo-controlled trial was conducted to determine the effects of sustained nicotine administration on behavior, cognition, and physiology. The results revealed improved learning during the nicotine treatment, persisted throughout washout. Memory, behavior, and global cognition were not significantly affected. Sustained administration of nicotine appeared to be safe, although sleep was significantly decreased [77].

In small doses, nicotine increased blood pressure and increased the activity of the gastric mucous membrane. In larger doses, it reduced blood pressure and lowers muscle tone of the gastrointestinal tract. Nicotine stimulated the respiratory and central nervous system [78].

Nicotine binds to nicotinic cholinergic receptors (nAChRs), nAChR complex is composed of five subunits and is found in both the peripheral and central nervous systems. In the mammalian brain, there were as many as nine α subunits ($\alpha 2$ to $\alpha 10$) and three β subunits ($\beta 2$ to $\beta 4$). The most abundant receptor subtypes in the brains of humans were $\alpha 4\beta 2$, $\alpha 3\beta 4$,

and α7 (homomeric). The α4β2(asterisk indicated possible presence of other subunits in the receptor) receptor subtype was predominant in the human brain and was believed to be the main receptor mediating nicotine dependence [79].

The α4 subunit appeared to be an important determinant of sensitivity to nicotine. The α3β4 nAChR was believed to mediate the cardiovascular effects of nicotine. The homomeric α7 nAChR was thought to be involved in rapid synaptic transmission and may played a role in learning and sensory gating [80-83].

Stimulation of central nAChRs by nicotine resulted in the release of avariety of neurotransmitters in the brain, most importantly dopamine. Nicotine caused the release of dopamine in the mesolimbic area, the corpus striatum, and the frontal cortex. Of particular importance was the dopaminergic neurons in the ventral tegmental area of the midbrain, and the release of dopamine in the shell of the nucleus accumbens, as this pathway appeared to be critical in drug-induced reward. Dopaminereleasesignalsapleasurableexperience,andwascriticaltothereinforcingeffectsof nicotine and other drugs of abuse. Dopamine release, during acute nicotine administration increased brain reward function [84-85].

Other neurotransmitters, including norepinephrine, acetylcholine, serotonin, γ-aminobutyric acid (GABA), glutamate, and endorphins, were released as well, mediating various behaviors of nicotine. The nicotine-mediated release of neurotransmitters occurred via modulation by presynaptic nAChRs, although direct release of neurotransmitters also occurred. Dopamine release was facilitated by nicotine-mediated augmentation of glutamate release and, with long-term treatment, by inhibition of GABA release [86-87].

Nicotine withdrawal was associated with a negative emotional state, including anxiety and the perception of increase distress, which may represented powerful stimuli to relapse to tobacco use. There was evidence that the activation of the extra-hypothalamic corticotropin-releasing factor (CRF)-CRF1 receptor system contributed to negative affect during nicotine withdrawal [88].

3.1. Toxicity and side effects

Acute toxicity study revealed that the LD_{50}ofhydroethanolic leaf extract was 5.82g/ kg in mice [69]. LD_{50} of nicotine in rat was 1mg/kg iv and 55mg orally.LD_{50} in dog was 1mg/kg and LD_{50} in horse was 200 to 300mg. Lethal doses of nicotine in adult human was 0.5 - 1mg/kg bw. Two to four drops pure nicotine were lethal (each drop: 23-33 mg).The lethal dose in children was 10 mg of nicotine [89-91].

The toxic effects of aqueous and methanolic extracts(10 mg/kg bw) of *Nicotiana tabacum* on haematological parameters and its histopathological effects on the brain and liver were studied in rats. There was a significant ($P<0.05$) decrease in body weight red blood cells (RBC), hematocrite, (HCT or PCV), haemoglobin (HGB) for aqueous extracts (7.45 ± 0.93, 14.90 ± 1.89, 44.70 ±5.60,respectively). Methanolic extracts of tobacco also significantly decreased the value of RBC, HCT, and HGB (6.63 ± 1.04, 13.27 ± 2.07 and 39.8 ± 6.27 respectively) when compared with the control group (7.72 ± 0.57, 15.43 ± 1.14 and 46.30 ± 3.43 respectively) but no significant ($P>0.05$) increase in mean cell volume (MCV), mean cell haemoglobin (MCH) and mean cell haemoglobin concentration (MCHC) for both extracts. The histopathological section of brain and liver showed neuronal and liver degeneration, necrosis and cirrhosis were recorded in aqueous and methanolic extract groups [92].

The tobacco plant, was responsible for more deaths than any other herb. Tobacco smoking caused over 3 million deaths a year worldwide, and if current smoking trends continued, the annual mortality will exceed 10 million by around 2030.Furthermore, mortality from cancers cardiovascular, respiratory and other diseases associated with smoking were still high. Undoubtedly, tobacco is the most important avoidable cause of premature death and disease in the world[22, 93-95].

Symptoms of an acute poisoning include dizziness, salivation, vomiting, diarrhea, trembling of the hands and feelings of weakness in the legs; very high dosages can lead rapidly to spasms, unconsciousness, cardiac arrest and respiratory failure. Poisonings occur in particular through the ingestion of cigarettes by children and through the handling of insecticides containing nicotine and in connection with the harvesting of tobacco. Nicotine patches also represented a danger for children [25].

4. Conclusion

The current review discussed the chemical constituents, pharmacological and toxicological characteristics of *Nicotiana tabacum*. Despite its wide pharmacological activities, it is not free from toxic effects. This review was designed to encourage researchers to conduct more studies for the optimal use of this plant medicinally.

Compliance with ethical standards

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