



CODEN (USA): IAJ PBB

ISSN: 2349-7750

INDO AMERICAN JOURNAL OF
PHARMACEUTICAL SCIENCESAvailable online at: <http://www.iajps.com>

Review Article

**PHYTOCHEMICAL CONSTITUENTS AND MEDICINAL
PROPERTIES OF *DIGITALIS LANATA* AND *DIGITALIS
PURPUREA*- A REVIEW****Ali Esmail Al-Snafi**

Department of Pharmacology, College of Medicine, Thi qar University, Iraq.

Received: 01 February 2017**Accepted:** 08 February 2017**Published:** 28 February 2017**Abstract:**

Digitalis lanata and *Digitalis purpurea* of the family Plantaginaceae were grown in Iraq. *Digitalis lanata* and *Digitalis purpurea* contains cardiac glycosides, volatile oil, fatty matter, starch, gum and sugars. They possessed cardiovascular, cytotoxic, antidiabetic, antioxidant, insecticidal, immunological, hepato, neuro and cardioprotective effects. This review highlights the chemical constituents and pharmacological effects of *Digitalis lanata* and *Digitalis purpurea*.

Keywords: *Digitalis lanata*, *Digitalis purpurea*, pharmacology, phytochemica**Corresponding author:****Ali Esmail Al-Snafi,**

Department of Pharmacology,

College of Medicine,

Thi qar University, Iraq.

Cell: +9647801397994.**E mail:** aboahmad61@yahoo.com

QR code



Please cite this article in press as Ali Esmail Al-Snafi, *Phytochemical Constituents and Medicinal Properties of Digitalis Lanata and Digitalis Purpurea- A Review*, Indo Am. J. P. Sci, 2017; 4(02).

INTRODUCTION:

Two thirds of the new chemicals identified yearly were extracted from higher plants. In the US, where chemical synthesis dominates the pharmaceutical industry, 25% of the pharmaceuticals are based on plant-derived chemicals. Seventy five percent of the world's population used plants for therapy and prevention [1]. However, plants are a valuable source of a wide range of secondary metabolites, which are used as pharmaceuticals, agrochemicals, flavours, fragrances, colours, biopesticides and food additives [2-35]. *Digitalis lanata* and *Digitalis purpurea* of the family Plantaginaceae were grown in Iraq. *Digitalis lanata* and *Digitalis purpurea* contains cardiac glycosides, volatile oil, fatty matter, starch, gum and sugars. They possessed cardiovascular, cytotoxic, antidiabetic, antioxidant, insecticidal, immunological, hepato, neuro and cardioprotective effects. This review will highlight the chemical constituents and pharmacological effects of *Digitalis lanata* and *Digitalis purpurea*.

Synonyms [36-37]:***Digitalis lanata***

Digitalis epiglottidea Brera ex Steud., *Digitalis eriostachya* Besser ex Rchb., *Digitalis lanata* var. *abbreviata* Hausskn., *Digitalis nova* Winterl ex Lindl., *Digitalis orientalis* Elmig. and *Digitalis winterli* Roth.

Digitalis purpurea

Digitalis alba Schrank, *Digitalis campbelliana* W. Baxter, *Digitalis carnea* Meigen & Weing., *Digitalis fucata* Ehrh., *Digitalis gloxinoides* Carrière, *Digitalis gyspergerae* Rouy, *Digitalis intermedia* Lapeyr., *Digitalis libertiana* Dumort., *Digitalis longiflora* Lej., *Digitalis media* Elmig., *Digitalis miniana* Samp., *Digitalis nevadensis* Kunze, *Digitalis purpurascens* Roth, *Digitalis purpurascens* Lej., *Digitalis purpurea* f. *alba* (Schrank) K. Werner, *Digitalis purpurea* var. *albiflora* Lej., *Digitalis purpurea* f. *alpina* K. Werner, *Digitalis purpurea* subsp. *bocquetii* Valdés, *Digitalis purpurea* f. *carnea* (Meigen & Weing.) K. Werner, *Digitalis purpurea* var. *gyspergerae* (Rouy) Fiori, *Digitalis purpurea* var. *humilis* Rouy, *Digitalis purpurea* f. *humilis* (Rouy) K. Werner, *Digitalis purpurea* var. *miniana* (Samp.) Cout., *Digitalis purpurea* var. *nevadensis* Amo, *Digitalis purpurea* var. *parviflora* Lej., *Digitalis purpurea* f. *parviflora* (Lej.) K. Werner, *Digitalis purpurea* var. *tomentosa* (Hoffmanns. & Link) Webb, *Digitalis purpurea* var. *valida* Merino, *Digitalis purpureolutea* G. Mey., *Digitalis speciosa* Salisb., *Digitalis thapsi* Bertero ex Nyman, *Digitalis thapsi* var. *intermedia* Lindl. and *Digitalis tomentosa* Hoffmanns. & Link.

Taxonomic classification:

Kingdom: Plantae; **Subkingdom:** Viridiplantae;
Infrakingdom: Streptophyta; **Superdivision:**

Embryophyta; **Division:** Tracheophyta; **Subdivision:** Spermatophytina; **Class:** Magnoliopsida; **Superorder:** Asteranae; **Order:** Lamiales; **Family:** Plantaginaceae; **Genus:** *Digitalis*; **Species:** *Digitalis lanata* (Grecian foxglove) and *Digitalis purpurea* (Purple foxglove) [38-39].

Common names[40-42]:***Digitalis lanata***

Arabic: Zahr Alkishteban, Asabi athara swfia, Kameia, Asabi Swfia; **English:** digitalis, Grecian foxglove, woolly digitalis, woolly foxglove; **French:** digitale laineuse; **German:** wolliger Fingerhut; **Spanish:** digital; **Swedish:** grekisk fingerborgsblomma.

Digitalis purpurea

Arabic: Asabi athara hamra, kafaz elthalab, digital erjwani, kameiat riz; **Ayurvedic:** Hritpatri, Tilapushpi; **Chinese:** mao di huang; **English:** purple foxglove, digitalis, foxglove, common foxglove, fairy fingers, fairy gloves; **Korean:** digitalriseu; **Swedish:** fingerborgsblomma.

Distribution:

Digitalis lanata is native to Europe, now it is cultivated in Asia-Temperate, Western Asia and Europe (Moldova, Austria, Czech Republic, Hungary, Slovakia, Albania, Bulgaria, Croatia, Greece, Romania, Serbia, Ukraine). *Digitalis purpurea* is thought to be native to West, South-West and West Central Europe. It is distributed in Africa (Morocco, Cape Verde, Madeira Islands, Canary Islands), Europe (Belgium, Germany, Finland, Ireland, Norway, Sweden, United Kingdom, Albania, Italy, France, Portugal, Spain, Czech Republic, Denmark and Croatia) [41-42].

Description [43-44]:***Digitalis lanata***

Digitalis is a biennial or perennial herb that grows up to about 1.2 meters height. **Flower and Fruit:** The inflorescence is long and densely flowered, with racemes facing all directions. The bracts are glandular-haired with ciliate edges. The flower structures are in fives. The sepals are fused, the calyx tubular. The petals are fused to a campanulate corolla, which is glandular-haired on, the outside, white with yellow-brown spots, 18 to 25 mm long and unevenly bilabiate. The upper lip has 4 points, and is flat and hem-like. The lower lip is almost as long as the corolla tube and is turned away from it. There are 4 stamens, often stretching out of the corolla tube. The ovaries are superior, 2-chambered, clavate, glandular-haired, gradually merging into the stigmas. The fruit is a 10 mm long septicidal, brittle capsule. The seeds are approximately 1.5 mm long and red-brown. **Leaves, Stem and Root:** *Digitalis lanata* is a herbaceous biennial or perennial, upright, up to 1.2 m high. The leaves are sessile, simple, narrow-lanceolate, 15 to 35 cm long, entire and ciliate in the upper area of the shoot axis.

The stem is upright, usually green, grooved-edged, usually glabrous below and long woolly-haired in the upper half. The plant has a primary root with no shoot-bearing roots.

Digitalis purpurea

Digitalis is a biennial or perennial herb that grows up to about 1.2 meters height. Flower and Fruit: The flowers are carmine red with white edged spots on the inside. The flowers appear in long hanging racemes. They have 5 free, short-tipped sepals. The corolla is about 4 cm long, campanulate, bilabiate with an obtuse upper lip and an ovate tip on the lower lip. The flower is glabrous on the outside and has a white awn on the inside. There are 2 long and 2 short stamens, and 1 superior ovary. The fruit is a 2-valved, ovate, glandular, villous capsule. The plant with a branched tap root. In the first year it develops a leaf rosette. In the second it produces a 2 m high, erect, unbranched, gray, tomentose stem. The leaves are alternate, ovate, tapering upward and petiolate. Almost all leaves are crenate; only the highest ones are entire-margined.

Traditional uses:

Earlier, *Digitalis* Species were used to treat ulcers, boils, abscesses, headaches and paralysis. Externally, *Digitalis* species were used for the granulation of poorly healing wounds and to cure ulcers. After William Withering work, the digoxin is isolated from *Digitalis* species as life-saving cardiac drug [40, 43].

Parts used medicinally:

***Digitalis lanata*:** The leaves are the medicinal part of the plant.

***Digitalis purpurea*:** The medicinal parts are the dried leaves (in powder form), the ripe dried seeds, the fresh leaves of the 1-year-old plant or the leaves of the 2-year-old plant collected at the beginning of flowering [43].

Chemical constituents:

Digitalis lanata and *Digitalis purpurea* contained cardiac glycosides, volatile oil, fatty matter, starch, gum and sugars [44]. Cardiac glycosides from plant sources have been known for long time. The Major plant derived cardiac glycosides were included digitoxin, digoxin, ouabain, oleandrin and proscillaridin, which were extracted from *Digitalis purpurea*, *Digitalis lanata*, *Strophanthus gratus*, *Nerium oleander* and *Urginea maritima*. Cardiac glycosides were consisted of a steroidal nucleus linked with a sugar at C3 and a lactone ring at C17. Various sugar and lactones provide a large number of cardiac glycosides that, based on their lactone moieties, they can be divided into two groups, cardenolides, which contain a five-membered unsaturated butyrolactone ring, and bufadienolides, which contain a six-membered unsaturated pyrone ring. The core steroidal portion of each molecule

has an A/B and C/D cisconformation, which has significant pharmacological impact, while, the attached sugars (glucose, galactose, mannose, rhamnose, and digitalose), affected the pharmacodynamic and pharmacokinetic characteristics of cardiac glycosides [45-46].

Digitalis lanata contained cardioactive steroid glycosides (cardenolides) (0.5 to 1.5%) including: [Aglycone digitoxigenin: including lanatoside A (0.05 to 0.25%) glucodigifucoside (0.01 to 0.15%), glucoe-vatromonoside (0.02 to 0.05%), digitoxin, alpha- and betaacetyldigoxin]; [Aglycone gitoxigenin: lanatoside B (0.01 to 0.15%), glucogitoroside (0.02 to 0.12%), *Digitalinum verum* (0.02 to 0.12%), gitoxin, alpha- and betaacetylgitoxin]; [Aglycone digoxigenin: lanatoside C (0.08 to 0.24%), desacetyl lanatoside C and digoxin]; [Aglycone diginatin: lanatoside D, diginatin, diginatin gitaloside]; [Aglycone gitaloxigenin: lanatoside E, glucoverodoxin (0.01 to 0.14%), glucoverodoxin (0.02 to 0.12%) and gitaloxin]; [Pregnane derivatives: including digifolein, glucodigifolein, diginin, digipronin, lanafolein and gitonine]; [Steroid saponins: including lanagitosides I and II, tigonin, desglucolanatigonin, aglycones including tigenin, digalogenin, digitogenin and gitogenin] [43]. Phenylethyl glycosides, maxoside (=2-(3,4-dihydroxyphenyl)ethyl O-b-d-glucopyranosyl-(1→3)-O-[b-d-glucopyranosyl-(1→6)]-b-d-glucopyranoside 4-[(2E)-3-(3,4-dihydroxyphenyl)prop-2-enoate]); 3-O-methylmaxoside (=2-(3,4-dihydroxy phenyl)ethyl O-β-dglucopyranosyl-(1→3)-O-[b-d-glucopyranosyl-(1→6)]-4-O-(E)-feruloyl-b-d-glucopyranoside; digilanosides A (=2-(3,4-dihydroxyphenyl)ethyl O-6-O-(E)-sinapoyl-b-d-glucopyranosyl-(1!3)-4-O-(E)-caffeoyl-b-d-glucopyranoside; and digilanoside B (=2-(3,4-dihydroxyphenyl)ethyl O-6-O-(E)-p-coumaroyl-b-d-glucopyranosyl-(1!3)-4-O-(E)-caffeoyl-b-d-glucopyranoside; 3) were isolated from the aerial parts of *Digitalis lanata* [47].

Digitalis purpurea contained cardioactive steroid glycosides (cardenolides 0.5 to 1.5%) including [Aglycone digitoxigenin: *purpurea* glycoside A (primary glycoside), digitoxin (secondary glycoside)]; [Aglycone gitoxigenin: *purpurea* glycoside B (primary glycoside), gitoxin (secondary glycoside)]; [Aglycone gitaloxigenin: glucoverodoxin, glucogitaloxin, gitaloxin]; [Pregnane glycosides: including digipurpurin, diginin, digitalonin]; [Steroid saponin: including desgalactotigonin, digitonine, *purpurea* agitoside]; [Anthracene derivatives: anthraquinones] [43]. Four different glycosides including acteoside, *purpurea* side A, calceolarioside B and plantainoside D were isolated from the leaves of *Digitalis purpurea* [48].

The minerals [Boron (B), Chromium (Cr), Manganese (Mn), Cobalt (Co), Nickel (Ni), Copper (Cu), Arsenic (As) and Lead (Pb)] in various plant parts of *Digitalis purpurea* and *Digitalis lanata* at pre- and post flowering stages were determined. The results revealed that the mineral concentrations in different parts were B 8.16 ± 0.04 to 27.18 ± 1.11 , Cr 7.30 ± 0.03 to 21.16 ± 0.20 , Mn 62.69 ± 1.45 to 247.27 ± 5.29 , Co 0.65 ± 0.08 to 6.13 ± 0.05 , Ni 9.19 ± 0.01 to 16.15 ± 0.05 , Cu 0.02 ± 0.0 to 25.27 ± 0.20 , As 0.83 ± 0.04 to 4.98 ± 0.06 and Pb 4.70 ± 0.02 to 8.19 ± 0.04 $\mu\text{g/g}$. The concentration of most of the minerals was higher at post flowering than that of pre flowering stage [49].

Pharmacological effects:

Cardiovascular effects:

Cardiac glycosides, are often called digitalis or digitalis glycosides, in particular digoxin and digitoxin, have been a cornerstone of the treatment of heart diseases for more than two centuries. However, the identification of angiotensin-converting enzyme inhibitors, β -adrenergic blockers and angiotensin-receptor blockers has significantly reduced their clinical use. The cardiac glycosides are with low therapeutic index. They possessed many cardiovascular effects by many mechanisms included [50-54]:

- Regulation of cytosolic calcium concentration: By inhibiting the Na^+/K^+ -adenosine triphosphatase (ATPase) enzyme, digitalis reduced the ability of the myocyte to actively pump Na^+ from the cell. This decreased the Na^+ concentration gradient and, consequently, the ability of the $\text{Na}^+/\text{Ca}^{2+}$ -exchanger to move calcium out of the cell. Furthermore, the higher cellular Na^+ is exchanged for extracellular Ca^{2+} by the $\text{Na}^+/\text{Ca}^{2+}$ -exchanger, increasing intracellular Ca^{2+} . A small but physiologically important increase occurred in free Ca^{2+} that is available at the next contraction cycle of the cardiac muscle, thereby increasing cardiac contractility. When Na^+/K^+ -ATPase is markedly inhibited by digitalis, the resting membrane potential may increase (-70 mV instead of -90 mV), which making the membrane more excitable and increasing the risk of arrhythmias (toxicity).

- Increased contractility of the cardiac muscle: Digitalis increased the force of cardiac contraction, causing cardiac output to more closely resemble that of the normal heart. Vagal tone was also enhanced, so both heart rate and myocardial oxygen demand decreased. Digitalis slowed conduction velocity through the AV node, making it useful for atrial fibrillation.

- Neurohormonal inhibition: Although the exact mechanism of this effect has not been elucidated, low-dose digitalis inhibited sympathetic activation with minimal effects on contractility. This effect was the reason a lower serum drug concentration

was targeted in heart failure with reduced ejection fraction.

Digoxin therapy was indicated in patients with severe heart failure with reduced ejection fraction after initiation of ACE inhibitor, β -blocker, and diuretic therapy. A low serum drug concentration of digoxin (0.5 to 0.8 ng/ml) was beneficial in heart failure with reduced ejection fraction and reduced heart failure admissions, along with improved survival. At higher serum drug concentrations, admissions are prevented, but mortality likely increased. Digoxin was not indicated in patients with diastolic or right sided heart failure unless the patient has concomitant atrial fibrillation or flutter.

- Electrophysiological effects: The major effect on cardiac rhythm of digitalis preparations was believed to be due to inhibition of the sodium pump. However, cells in various parts of the heart showed differing sensitivities to digitalis, and both direct and neurally mediated effects were occurred. Indeed, at therapeutic levels, these drugs decreased automaticity and increased maximum diastolic potential, effects that can be blocked by atropine, whereas higher (toxic) concentrations decreased diastolic potentials and increased automaticity. Similarly, the toxic arrhythmogenic effects of the cardiac glycosides were due to a combination of direct effects on the myocardium and neurally mediated increases in autonomic activity. Both systolic and diastolic $[\text{Ca}^{2+}]_i$ increased during digitalis-induced arrhythmias, increases that leading to the idea that intracellular (Ca^{2+} overload) contributes to the observed arrhythmogenic effects. Spontaneous cycles of Ca^{2+} release and reuptake then ensued, resulting in after depolarizations and after contractions. The after depolarization was the result of a Ca^{2+} -activated transient inward current and was thought to be the macroscopic manifestation of Ca^{2+} -activated nonspecific cation channels, plus $\text{Na}^+/\text{Ca}^{2+}$ exchange current [55].

Cytotoxic effects:

Extracts of *Digitalis lanata* and *Digitalis purpurea* were examined for anticancer activity in 10 human tumor cell lines. They produced cytotoxic effects, but the activity profiles were uncorrelated with those of the standard drugs, possibly indicating new pathways of drug-mediated cell death [56].

The saponin digitonin, the aglycone digitoxigenin and five cardiac glycosides were evaluated for cytotoxicity using primary cultures of tumor cells from patients and a human cell line panel (representing different cytotoxic drug-resistance patterns). Of these compounds, proscillaridin A was the most potent (IC_{50} : 6.4 – 76 nM), followed by digitoxin, and then ouabain, digoxin, lanatoside C, digitoxigenin and digitonin. Correlation analysis of the log IC_{50} values for the cell lines in the panel showed that compound cytotoxicity was only slightly influenced by resistance mechanisms that

involved P-glycoprotein, topoisomerase II, multidrug resistance-associated protein and glutathione-mediated drug resistance. Digitoxin and digoxin expressed selective toxicity against solid tumor cells, while proscillaridin A expressed no selective toxicity against either solid or hematological tumor cells [57].

The cytotoxic activity of 15 cardenolide glycosides isolated from *Digitalis purpurea* seeds was evaluated against HL-60 leukemia cells. 4 compounds showed potent cytotoxicity against HL-60 cells with IC_{50} values of 0.060, 0.069, 0.038, and 0.034 μ M. Three of these compounds also exhibited potent cytotoxic activity against HepG2 human liver cancer cells with IC_{50} values of 0.38, 0.79, and 0.71 μ M. An investigation of the structure-activity relationship showed that the cytotoxic activity was reduced by the introduction of a hydroxy group at C-16 of the digitoxigenin aglycone, methylation of the C-3' hydroxy group at the fucopyranosyl moiety, and acetylation of the C-3' hydroxy group at the digitoxopyranoyl moiety [58].

The steroidal cardiac Na^+/K^+ ATPase inhibitors were potent anti-cancer compounds in multiple cell lines from different tumor panels including multi-drug resistant cells. Of many synthetic steroidal cardiac, the most potent compound identified was 3-[(R)-3- pyrrolidinyl]oxime derivative, it showed outstanding potencies (as measured by GI_{50} , TGI and LC_{50} values) in most cells *in vitro*, it was selectively cytotoxic in cancer versus normal cells showing a therapeutic index of 31.7 and exhibited significant tumor growth inhibition in prostate and lung xenografts *in vivo* [59].

Numerous other studies have confirmed the antiproliferative and apoptotic effects of cardiac glycosides in several cancer cell lines, including prostate, melanoma, pancreatic, leukaemia, neuroblastoma, and tumors of urinary and respiratory systems [57, 60-76].

Many epidemiological studies revealed that breast cancer tissue samples from congestive heart failure patients treated with cardiac glycoside therapy showed more benign characteristics and need less mastectomy than samples taken from patients who were not used cardiac glycosides [77]. Mortality rate in patients treated with cardiac glycoside therapy was also less than that in patients who were not used cardiac glycosides [78].

Regarding the mechanisms of anticancer effects of cardiac glycosides, it appeared that digitoxin induced cell cycle arrest in G2/M phase via down-regulation of cyclin B1, cdc2 and surviving and increased the intracellular Ca^{2+} concentration. Digoxin increased intracellular Ca^{2+} concentration and induced DNA topoisomerases I and II and induced cell cycle arrest via the up-regulation of HIF-1 α . Ouabain depleted Na^+/K^+ ATPase and up-regulated p21, increased intracellular Ca^{2+}

concentration and inhibited DNA topoisomerases I and II. Oleandrin attenuated NF- κ B, JNK and AP-1 activation. Bufalin induced cell cycle arrest in G2/M phase via up-regulation of p21 WAF1 and p53 and the down-regulation of cyclin D, and inhibited DNA topoisomerases I and II. Proscillaridin A, inhibited DNA topoisomerases I and II and increased intracellular Ca^{2+} [70, 79-87].

Inhibition of IL-8:

Oleandrin, a cardiac glycoside potentially inhibited IL-8-, formyl peptide (FMLP)-, EGF-, or nerve growth factor (NGF)-, but not IL-1- or TNF-induced NF- κ B activation in macrophages. Oleandrin inhibited IL-8-, but not TNF-induced NF- κ B-dependent genes expression. Oleandrin inhibited the binding of IL-8, EGF, or NGF, but not IL-1 or TNF. It decreased almost 79% IL-8 binding without altering affinity towards IL-8 receptors and this inhibition of IL-8 binding was observed in isolated membrane. The IL-8, anti-IL-8Rs antibodies, or protease inhibitors were unable to protect oleandrin-mediated inhibition of IL-8 binding. Phospholipids significantly protected oleandrin-mediated inhibition of IL-8 binding thereby restoring IL-8-induced NF- κ B activation. Oleandrin altered the membrane fluidity as detected by microviscosity parameter and a decrease in diphenylhexatriene, a lipid binding fluorophore binding in a dose-dependent manner. The authors concluded that oleandrin inhibits IL-8-mediated biological responses in diverse cell types by modulating IL-8Rs through altering membrane fluidity and microviscosity. Accordingly, oleandrin might help to regulate IL-8-mediated biological responses involved in inflammation, angiogenesis, tumorigenesis, metastasis, and neovascularization [88].

Digitoxin, at sub nM concentrations, can suppress hypersecretion of IL-8 from cultured cystic fibrosis (CF) lung epithelial cells. Certain other cardiac glycosides were also active but with much less potency. The specific mechanism of digitoxin action was included blocking phosphorylation of the inhibitor of NF- κ B (I κ B α). I κ B α phosphorylation was a required step in the activation of the NF- κ B signaling pathway and the subsequent expression of IL-8. Digitoxin also possessed effects on global gene expression in CF cells [89].

Hepato-, neuro- and cardio- protective effects:

Four different glycosides (acteoside, purpureaside A, calceolarioside B and plantainoside D) isolated from the leaves of *Digitalis purpurea* were studied for their abilities to induce glutathione S-transferase (GST) and their protective efficiencies against aflatoxin B1-induced cytotoxicity in H4IIE cells. Of these four glycosides, acteoside significantly

inhibited the cytotoxicity induced by aflatoxin B1 (AFB1) and also selectively increased GSTalpha protein levels. Reporter gene analysis using an antioxidant response element (ARE) containing construct and subcellular fractionation assays, revealed that GST alpha induction by acteoside might be associated with Nrf2/ARE activation [48]. The neuroprotective action of cardiac glycoside neriifolin was evaluated in ischemic stroke. Neriifolin provided significant neuroprotection in a neonatal model of hypoxia/ischemia and in a middle cerebral artery occlusion model of transient focal ischemia [90].

The heart protective effects of ouabain against ischemia-reperfusion injury, through activation of the Na^+K^+ -ATPase/c-Src receptor complex, was studied. In Langendorff-perfused rat hearts, a short (4 min) administration of ouabain 10 μM followed by an 8-minute washout before 30 min of global ischemia and reperfusion, improved cardiac function, decreased lactate dehydrogenase release and reduced infarct size by 40%. Western blot analysis revealed that ouabain activated the cardioprotective phospholipase C gamma1/protein kinase Cepsilon (PLC-gamma1/PKCepsilon) pathway. Pre-treatment of the hearts with the Src kinase family inhibitor 4-amino-5-(4-chlorophenyl)-7-(t-butyl)pyrazolol[3,4-d]pyrimidine (PP2) blocked not only ouabain-induced activation of PLC-gamma1/PKCepsilon pathway, but also cardiac protection. The protection was also blocked by a PKCepsilon translocation inhibitor peptide (PKCepsilon TIP) [91].

Antidiabetic effect:

Digitonin, a saponin from the seeds of *Digitalis purpurea*, improved the glucose tolerance and possessed beneficial effects on serum lipids by improve antioxidant activity in rats [92].

Antioxidant effect:

The scavenging activity of alcoholic extract of *Digitalis purpurea* was measured using DPPH and the total antioxidant capacity of *Digitalis purpurea* was measured by phosphomolybdate using ascorbic acid as the standard. *Digitalis purpurea* 1mg/ml showed 94.25% DPPH scavenging activity and 92.28% total anti-oxidant activity [93].

Insecticidal effect:

Studying of insecticidal activity of alcoholic extract of *Digitalis purpurea* against *T. castaneum* revealed that the percentage mortality of *T. castaneum* was 60%, at 100 mg/2 ml of alcoholic extract of *Digitalis purpurea* [93].

Adverse effects and toxicity:

Digitalis is a toxic plant. At low serum drug concentrations, digitalis was well tolerated. However, it characterized by a very narrow therapeutic index, and digitalis toxicity was one of the most common adverse drug reactions leading to hospitalization. Anorexia, nausea, and vomiting

may be initial indicators of toxicity, they occurred due to a direct action of digitalis on the CTZ. Patients may also experience blurred vision, yellowish vision (xanthopsia), and various cardiac arrhythmias. Diarrhoea may be noted, as may abdominal discomfort, or pain, headache, malaise and drowsiness were common symptoms, neuralgic pain may be the earliest most severe, or the sole symptom, digitalis delirium, may occur with confusion, disorientation, aphasia and mental clouding. Toxicity can often be managed by discontinuing digitalis, determining serum potassium levels, and, if indicated, replenishing potassium. Decreased levels of serum potassium (hypokalemia) predispose a patient to digitalis toxicity, since digitalis normally competes with potassium for the same binding site on the Na^+K^+ -ATPase pump. However, the single most frequent cause of intoxication was the concurrent administration of thiazide or loop diuretics that cause hypokalaemia. Severe toxicity resulting in ventricular tachycardia may required administration of antiarrhythmic drugs and the use of antibodies to digoxin (digoxin immune Fab), which bind and inactivate the drug. With the use of a lower serum drug concentration in heart failure, toxic levels were infrequent. Digoxin was a substrate of P-gp, and inhibitors of P-gp, such as clarithromycin, verapamil, and amiodarone, can significantly increase digoxin levels, necessitating a reduced dose of digoxin. Digoxin should also be used with caution with other drugs that slow AV conduction, such as β -blockers, verapamil, and diltiazem [50, 55].

CONCLUSION:

The current review discussed the chemical constituents and pharmacological effects of *Digitalis lanata* and *Digitalis purpurea* as an important medicinal plants with wide range of medicinal uses.

REFERENCES:

- 1.Orhan IE . Biotechnological production of plant secondary metabolites. Bentham ebook, 2012: 107.
- 2.Al-Snafi AE. Medicinal plants possessed anti-inflammatory antipyretic and analgesic activities (part 2)- plant based review. Sch Acad J Pharm 2016; 5(5): 142-158. <http://saspublisher.com/wp-content/uploads/2016/06/SAJP-55142-158.pdf>
- 3.Al-Snafi AE. Medicinal plants affected reproductive systems (part 2) - plant based review. Sch Acad J Pharm 2016; 5(5): 159-174.
- 4.Al-Snafi AE. Medicinal plants with anticancer effects (part 2)- plant based review. Sch Acad J Pharm 2016; 5(5): 175-193.
- 5.Al-Snafi AE. Antiparasitic, antiprotozoal, molluscicidal and insecticidal activity of medicinal plants (part 2) – plant based review. Sch Acad J Pharm 2016; 5(6): 194-207.

6. Al-Snafi AE. Medicinal plants with antidiabetic effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 49-61.
7. Al-Snafi AE. Medicinal plants with antioxidant and free radical scavenging effects (part 2): plant based review. IOSR Journal Of Pharmacy 2016; 6(7): 62-82.
8. Al-Snafi AE. Medicinal plants with antimicrobial activities (part 2): Plant based review. Sch Acad J Pharm 2016; 5(6): 208-239.
9. Al-Snafi AE. Medicinal plants with cardiovascular effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 43-62. <http://www.iosrphr.org/papers/v6i7V3/E067034362.pdf>
10. Al-Snafi AE. Detoxification capacity and protective effects of medicinal plants (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 63-84.
11. Al-Snafi AE. Beneficial medicinal plants in digestive system disorders (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(7): 85-92. <http://www.iosrphr.org/papers/v6i7V3/G067038592.pdf>
12. Al-Snafi AE. A review of medicinal plants with broncho-dilatory effect-Part 1. Scholars Academic Journal of Pharmacy, 2015; 5(7): 297-304. <http://saspublisher.com/wp-content/uploads/2016/08/SAJP-57297-304.pdf>
13. Al-Snafi AE. Medicinal plants with central nervous effects (part 2): plant based review. IOSR Journal of Pharmacy 2016; 6(8): 52-75. <http://www.iosrphr.org/papers/v6i8V1/G068015275.pdf>
14. Al-Snafi AE. Immunological effects of medicinal plants: A review (part 2). Immun Endoc & Metab Agents in Med Chem 2016; 16(2): 100-121. <http://www.eurekaselect.com/146338>
15. Al-Snafi AE. Medicinal plants affected male and female fertility (part 1)- A review. IOSR Journal of Pharmacy 2016; 6(10): 11-26. www.iosrphr.org/papers/v6i10V3/C0610031126.pdf
16. Al-Snafi AE. Antiparasitic effects of medicinal plants (part 1)- A review. IOSR Journal of Pharmacy 2016; 6(10): 51-66. <http://www.iosrphr.org/papers/v6i10V3/H0610035166.pdf>
17. Al-Snafi AE. Antimicrobial effects of medicinal plants (part 3): plant based review. IOSR Journal of Pharmacy 2016; 6(10): 67-92. <http://www.iosrphr.org/papers/v6i10V3/I0610036792.pdf>
18. Al-Snafi AE. The pharmacological and toxicological effects of *Coronilla varia* and *Coronilla scorpioides*: A review. The Pharmaceutical and Chemical Journal 2016; 3(2): 105-114.
19. Al-Snafi AE. Pharmacological activities of *Cotoneaster racemiflorus*- A review. The Pharmaceutical and Chemical Journal 2016; 3(2):98-104. <http://tpcj.org/download/vol-3-iss-3-2016/TPCJ2016-03-03-98-104.pdf>
20. Al-Snafi AE. The constituents and pharmacology of *Corchorus aestuans*: A review. The Pharmaceutical and Chemical Journal 2016; 3(4):208-214. <http://tpcj.org/download/vol-3-iss-4-2016/TPCJ2016-03-04-208-214.pdf>
21. Al-Snafi AE. The chemical constituents and pharmacological activities of *Cymbopogon schoenanthus*: A review. Chemistry Research Journal 2016; 1(5):53-61.
22. Al-Snafi AE. Traditional uses, constituents and pharmacological effects of *Cuscuta planiflora*. The Pharmaceutical and Chemical Journal 2016; 3(4): 215-219. <http://tpcj.org/download/vol-3-iss-4-2016/TPCJ2016-03-04-215-219.pdf>
23. Al-Snafi AE. A review on *Dodonaea viscosa*: A potential medicinal plant. IOSR Journal of Pharmacy 2017; 7(2): 10-21.
24. Al-Snafi AE. The pharmacology and medical importance of *Dolichos lablab* (*Lablab purpureus*)- A review. IOSR Journal of Pharmacy 2017; 7(2): 22-30.
25. Al-Snafi AE. Pharmacological and therapeutic importance of *Desmostachya bipinnata*- A review. Indo Am J P Sci 2017; 4(01): 60-66
26. Al-Snafi AE. Chemical constituents and pharmacological effects of *Eryngium creticum*- A review. Indo Am J P Sci 2017; 4(01): 67-73. [http://iajps.com/pdf/january2017/10.%20Ali%20Es mail%20Al-Snafi,IAJPS%202017,%20\(01\),%2067-73.pdf](http://iajps.com/pdf/january2017/10.%20Ali%20Es mail%20Al-Snafi,IAJPS%202017,%20(01),%2067-73.pdf)
27. Snafi,IAJPS%202017,%20(01),%2067-73.pdf
28. Al-Snafi AE. The pharmacology of *Equisetum arvense*- A review. IOSR Journal of Pharmacy 2017; 7(2): 31-42.
29. Al-Snafi AE. A review on *Erodium cicutarium*: A potential medicinal plant. Indo Am J P Sci 2017; 4(01): 110-116.
30. Al-Snafi AE. Pharmacology of *Echinochloa crus-galli* - A review. Indo Am J P Sci 2017; 4(01): 117-122.
31. Al-Snafi AE. The pharmacological potential of *Dactyloctenium aegyptium*- A review. Indo Am J P Sci 2017; 4(01): 153-159.
32. Al-Snafi AE. Chemical constituents, pharmacological and therapeutic effects of *Eupatorium cannabinum*- A review. Indo Am J P Sci 2017; 4(01): 160-168.
33. Al-Snafi AE. Nutritional and therapeutic importance of *Daucus carota*- A review. IOSR Journal of Pharmacy 2017; 7(2): 72-88.
34. Al-Snafi AE. Chemical constituents and pharmacological effects of *Dalbergia sissoo* - A review. IOSR Journal of Pharmacy 2017; 7(2): 59-71.
35. Al-Snafi AE. Medical importance of *Datura fastuosa* (syn: *Datura metel*) and *Datura stramonium* - A review. IOSR Journal of Pharmacy 2017; 7(2):43-58.

36. Al-Snafi AE. A review on *Dodonaea viscosa*: A potential medicinal plant. IOSR Journal of Pharmacy 2017; 7(2): 10-21.
37. The plant list, a working list of all plant species, *Digitalis lanata*, <http://www.theplantlist.org/tpl1.1/record/kew-2768027>
38. The plant list, a working list of all plant species, *Digitalis purpurea*, <http://www.theplantlist.org/tpl/record/kew-2768087>
39. ITIS report, *Digitalis lanata*, http://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN&search_value=33583
40. ITIS report, *Digitalis purpurea*, http://www.itis.gov/servlet/SingleRpt/SingleRpt?search_topic=TSN&search_value=33585
41. Khare CP. Indian medicinal plants: An illustrated dictionary. Springer Publication. 2007: 214.
42. U.S. National Plant Germplasm System, *Digitalis purpurea*, <https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?13986>
43. U.S. National Plant Germplasm System, *Digitalis lanata*, <https://npgsweb.ars-grin.gov/gringlobal/taxonomydetail.aspx?13979>
44. PDR for herbal medicines. Medical Economics Company, Inc. at Montvale, 2000: 248-252.
45. Reddy BA. Digitalis therapy in patients with congestive heart failure. International Journal of Pharmaceutical Sciences Review and Research 2010;3(2): 90-95.
46. Prassas I and Diamandis EP. Novel therapeutic applications of cardiac glycosides. Nature reviews. Drug discovery 2008;7: 926-95.
47. Schönfeld W, Weiland J, Lindig C, Masnyk M, Kabat MM, Kurek A, Wicha J and Repke KR. The lead structure in cardiac glycosides is 5a,14a-androstane-3a14-diol. Naunyn-Schmiedeberg's Archives of Pharmacology 1985; 329: 414-426.
48. Kirmizibekmez H, Celep E, Masullo M, Bassarello C, Ilada EY and Piacente S. Phenylethyl glycosides from *Digitalis lanata*. Helvetica Chimica Acta 2009; 92: 1845-1852.
49. Lee JY, Woo E and Kang KW. Screening of new chemopreventive compounds from *Digitalis purpurea*. Pharmazie 2006; 61(4):356-358.
50. Negi SJ, Bisht VK, Bhandari AK and Sundriyal RC. Determination of mineral contents of *Digitalis purpurea* L. and *Digitalis lanata* Ehrh. Journal of Soil Science and Plant Nutrition 2012; 12 (3): 463-469.
51. Whalen K, Finkel R and Panavelil TA. Lippincott illustrated reviews: pharmacology, 6th Ed. Wolters Kluwer 2015: 263-265.
52. Kaplan JH. Biochemistry of Na, K-ATPase. Annu Rev Biochem 2002; 71: 511-535.
53. Smith TW. The fundamental mechanism of inotropic action of digitalis. Therapie 1989; 44: 431-435.
54. Jorgensen PL, Hakansson KO and Karlsh SJ. Structure and mechanism of Na, K-ATPase: functional sites and their interactions. Annu Rev Physiol 2003; 65: 817-849.
55. Mason DT and Braunwald E. Studies on digitalis, X: effects of ouabain on forearm vascular resistance and venous tone in normal subjects and in patients in heart failure. J Clin Invest 1964; 43:532-543.
56. Hauptman PJ and Kelly RA. Cardiovascular drugs, Digitalis. Circulation 1999; 99: 1265-1270.
57. Lindholm P, Gullbo J, Claesson P, Göransson U, Johansson S, Backlund A, Larsson R and Bohlin L. Selective cytotoxicity evaluation in anticancer drug screening of fractionated plant extracts. J Biomol Screen 2002; 7(4): 333-340.
58. Johansson S, Lindholm P, Gullbo J, Larsson R, Bohlin L and Claesson P. Cytotoxicity of digitoxin and related cardiac glycosides in human tumor cells. Anticancer Drugs 2001; 12(5):475-483.
59. Kuroda M, Kubo S, Matsuo Y, Atou T, Satoh J, Fujino T, Hayakawa M and Mimaki Y. New cardenolide glycosides from the seeds of *Digitalis purpurea* and their cytotoxic activity. Biosci Biotechnol Biochem 2013; 77(6):1186-1192.
60. Dimas K, Papadopoulou N, Baskakis C, Prousis KC, Tsakos M, Alkahtani S, Honisch S, Lang F, Calogeropoulou T, Alevizopoulos K and Stournaras C. Steroidal cardiac Na⁺/K⁺ ATPase inhibitors exhibit strong anti-cancer potential *in vitro* and in prostate and lung cancer xenografts *in vivo*. Anticancer Agents Med Chem 2014; 14(5):762-770.
61. Haux J, Klepp O, Spigset O and Tretli S. Digitoxin medication and cancer; case control and internal dose-response studies. BMC Cancer 2001;1:11.
62. Lopez-Lazaro M *et al.* Digitoxin inhibits the growth of cancer cell lines at concentrations commonly found in cardiac patients. J Nat Prod 2005; 68: 1642-1645
63. McConkey DJ, Lin Y, Nutt LK, Ozel HZ and Newman RA. Cardiac glycosides stimulate Ca²⁺ increases and apoptosis in androgen-independent, metastatic human prostate adenocarcinoma cells. Cancer Res 2000; 60: 3807-3812.
64. Huang YT, Chueh SC, Teng CM and Guh JH. Investigation of ouabain-induced anticancer effect in human androgen-independent prostate cancer PC-3 cells. Biochem Pharmacol 2004; 67: 727-733.
65. Yeh JY, Huang WJ, Kan SF and Wang PS. Effects of bufalin and cinobufagin on the proliferation of androgen dependent and independent prostate cancer cells. Prostate 2003; 54: 112-124.
66. Newman RA *et al.* Oleandrin-mediated oxidative stress in human melanoma cells. J Exp Ther Oncol 2006; 5: 167-181.
67. Newman RA *et al.* Autophagic cell death of human pancreatic tumor cells mediated by

oleandrin, a lipid-soluble cardiac glycoside. *Integr Cancer Ther* 2007; 6: 354–364.

68.Mijatovic T *et al.* The cardenolide UNBS1450 is able to deactivate nuclear factor κ B-mediated cytoprotective effects in human non-small cell lung cancer cells. *Mol Cancer Ther* 2006; 5: 391–399.

69.Watabe M, Kawazoe N, Masuda Y, Nakajo S and Nakaya K. Bcl-2 protein inhibits bufalin-induced apoptosis through inhibition of mitogen-activated protein kinase activation in human leukemia U937 cells. *Cancer Res* 1997; 57: 3097–3100.

70.Frese S *et al.* Cardiac glycosides initiate Apo2L/TRAIL-induced apoptosis in non-small cell lung cancer cells by up-regulation of death receptors 4 and 5. *Cancer Res* 2006; 66: 5867–5874.

71.Elbaz HA, Stueckle TA, Wang HY, O'Doherty GA, Lowry DT, Sargent LM, Wang L and Dinu CZ, Rojanasakul Y. Digitoxin and a synthetic monosaccharide analog inhibit cell viability in lung cancer cells. *Toxicology and Applied Pharmacology* 2012; 258: 51–60.

72.Raghavendra PB, Sreenivasan Y, Ramesh GT and Manna SK. Cardiac glycoside induces cell death via FasL by activating calcineurin and NF-AT, but apoptosis initially proceeds through activation of caspases. *Apoptosis* 2007; 12: 307–318.

73.Masuda Y *et al.* Bufalin induces apoptosis and influences the expression of apoptosis-related genes in human leukemia cells. *Leuk Res* 1995; 19: 549–556.

74.Daniel D, Susal C, Kopp B, Opelz G and Terness P. Apoptosis-mediated selective killing of malignant cells by cardiac steroids: maintenance of cytotoxicity and loss of cardiac activity of chemically modified derivatives. *Int Immunopharmacol* 2003; 3: 1791–1801.

75.Jing Y *et al.* Selective inhibitory effect of bufalin on growth of human tumor cells *in vitro*: association with the induction of apoptosis in leukemia HL-60 cells. *Jpn J Cancer Res* 1994; 85: 645–651.

76.Kulikov A, Eva A, Kirch U, Boldyrev A and Scheiner-Bobis G. Ouabain activates signaling pathways associated with cell death in human neuroblastoma. *Biochim Biophys Acta* 2007; 1768: 1691–1702.

77.Kawazoe N, Watabe M, Masuda Y, Nakajo S and Nakaya K. Tiam1 is involved in the regulation of bufalin-induced apoptosis in human leukemia cells. *Oncogene* 1999; 18: 2413–2421.

78.Stenkvis B. Evidence of a modifying influence of heart glucosides on the development of breast cancer. *Analytical and Quantitative Cytology* 1980; 2: 49–54.

79.Goldin AG, Safa AR: Digitalis and cancer. *Lancet* 1984;1: 1134.

80.Yang P, Chan D, Vijjeswarapu M, Cartwright C, Cohen L, Meng Z, Liu L and Newman RA. Anti-proliferative activity of Huachansu, a Bufo toad

skin extract, against human malignant melanoma cells. *Proceeding of American Association Cancer Research* 2006: 47

81.Jiang Y, Zhang Y, Luan J, Duan H, Zhang F, Yagasaki K and Zhang G. Effects of bufalin on the proliferation of human lung cancer cells and its molecular mechanisms of action. *Cytotechnology* 2010; 62: 573–83.

82.Tian J, Li X, Liang M, Liu L, Xie JX, Ye Q, Kometiani P, Tillekeratne M, Jin R and Xie Z. Changes in sodium pump expression dictate the effects of ouabain on cell growth. *Journal of Biological Chemistry* 2009; 284: 14921–14929.

83.Yeh JY, Huang WJ, Kan SF and Wang PS. Inhibitory effects of digitalis on the proliferation of androgen dependent and independent prostate cancer cells. *Journal of Urology* 2001; 166: 1937–42.

84.Winnicka K, Bielawski K, Bielawska A and Surazyński A. Antiproliferative activity of derivatives of ouabain, digoxin and proscillaridin A in human MCF-7 and MDAMB-231 breast cancer cells. *Biological and Pharmaceutical Bulletin* 2008;31 1131–1140.

85.Zhang H, Qian DZ, Tan YS, Lee K, Gao P, Ren YR, Rey S, Hammers H, Chang D, Pili R, Dang CV, Liu JO and Semenza GL. Digoxin and other cardiac glycosides inhibit HIF-1 α synthesis and block tumor growth. *Proceedings of the National Academy of Sciences of the United States of America* 2008;105: 19579–19586.

86.Sreenivasan Y, Sarkar A and Manna SK. Oleandrin suppresses activation of nuclear transcription factor- κ B and activator protein-1 and potentiates apoptosis induced by ceramide. *Biochemical Pharmacology* 2003; 66: 2223–2239.

87.Manna SK, Sah NK, Newman RA, Cisneros A and Aggarwal BB. Oleandrin suppresses activation of nuclear transcription factor- κ B, activator protein-1, and c-Jun NH2 terminal kinase. *Cancer Research* 2000; 60: 3838–3847.

88.Hashimoto S, Jing Y, Kawazoe N, Masuda Y, Nakajo S, Yoshida T, Kuroiwa Y and Nakaya K. Bufalin reduces the level of topoisomerase II in human leukemia cells and affects the cytotoxicity of anticancer drugs. *Leukemia Research* 1997; 21: 875–883.

89.Manna SK, Sreenivasan Y and Sarkar A. Cardiac glycoside inhibits IL-8-induced biological responses by downregulating IL-8 receptors through altering membrane fluidity. *J Cell. Physiol* 2006; 207(1): 195–207.

90.Srivastava M, Eidelman O, Zhang J, Pawletz C, Caohuy H, Yang Q, Jacobson KA, Heldman E, Huang W, Jozwik C, Pollard BS and Pollard HB. Digitoxin mimics gene therapy with CFTR and suppresses hypersecretion of IL-8 from cystic fibrosis lung epithelial cells. *Proc Natl Acad Sci U S A* 2004; 101(20): 7693–7698.

91.Wang JK, Portbury S, Thomas MB, Barney S, Ricca DJ, Morris DL, Warner DS and Lo DC.

Cardiac glycosides provide neuroprotection against ischemic stroke: discovery by a brain slice-based compound screening platform. *Proc Natl Acad Sci USA* 2006; 103(27): 10461-10466.

92. Pierre SV, Yang C, Yuan Z, Seminerio J, Mouas C, Garlid KD, Dos-Santos P and Xie Z. Ouabain triggers preconditioning through activation of the Na^+ , K^+ -ATPase signaling cascade in rat hearts. *Cardiovasc Res* 2007; 73(3): 488-496.

93. Ebaid GM, Faine LA, Diniz YS, Rodrigues HG, Galhardi CM, Ribas BO, Fernandes AA and Novelli EL. Effects of digitonin on hyperglycaemia and dyslipidemia induced by high-sucrose intake. *Food Chem Toxicol* 2006; 44(2): 293-299.

94. Ahmad M, Saeed F, Jahan MN. Evaluation of insecticidal and anti-oxidant activity of selected medicinal plants. *Journal of Pharmacognosy and Phytochemistry* 2013; 2 (3): 153-158.