

Contribution of Ethnopharmacology in Ameliorating Toxicity of Vital Organs

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SUMMARY

Ethnopharmacology is an integrated system of traditional medicines which are extracted from plants. These traditional medicines are employed as therapeutic agents owing to their abrogative potential against different diseases. These drugs are extensively studied to elucidate their mitigative properties against various sorts of diseases. Vital organs such as the lungs, kidney, liver, and heart are continuously exposed to several toxicities due to various sorts of toxicants which include environmental contamination, xenobiotics, and underlying conditions of particular diseases. Various sorts of Ethnopharmacological drugs are extensively used as ameliorative agents against liver, renal, lung, heart, and testicular toxicities in both humans and animals. Furthermore, various drug and food regulatory authorities such as WHO approved thousands of ethnopharmacological drugs as safe agents for oral intake. Overall, the findings highlight the potential of ethnopharmacological drugs as a source of new therapeutic approaches for the treatment of vital organ toxicity in humans and animals. In conclusion, ethnopharmacological drugs have shown promising results in mitigating the effects of vital organ toxicity. Further research is needed to fully understand the mechanisms of action and potential therapeutic benefits of these drugs. This chapter will encompass all the aspects of ethnopharmacological drugs and their role in the amelioration of vital organ toxicity.

INTRODUCTION

Ethnopharmacology is an integrated study associated with the analysis of traditional medicines and their biological role on the basis of their description, observation as well as experimental examination (Rivier & Bruhn 1979). The definition was later modified by Bruhn & Holmstedt (1981) as “ethnopharmacology is a multidisciplinary scientific investigation of bioactive substances that have been conventionally utilized or identified by man”. According to Fabricant & Farnsworth (2001), ethnopharmacology is an exceptionally diversified field that involves pharmacology, botany, chemistry, and biochemistry as well as various other subjects such as linguistics, history, archaeology, and anthropology. Ethnopharmacology was initially introduced in 1967 at an international conference held in San Francisco to

emphasize the multidisciplinary approach of conventional psychotropic drugs (Efron et al., 1967).

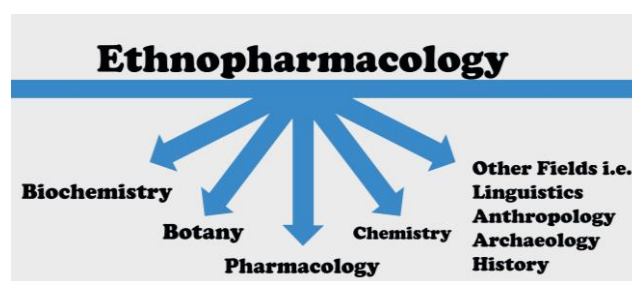


Fig 1. Diverse fields in ethnopharmacology

Traditional medicines vary in different regions as well as countries of the world and entail an extensive range of therapies and practices. These medicines are referred to as complementary or alternative medicines (Khamkar et al., 2015). About 70-80 percent people of in developed countries use

complementary medicine because they assume that these medicines are totally organic as well as risk-free and can be used as a treatment for chronic, painful, or fatal diseases (UNESCO, 2013). From 1981 to 2007, major sources of active components of medicine were natural products and more than half of the drugs approved since 1994 were extracted from natural products. Furthermore, 13 drugs obtained from natural resources were permitted during 2005-2007 (Harvey, 2008). During the time period of 1981-2002, almost 75 percent of anti-infectious medicines and 60 percent of anticancer remedies were obtained from natural sources, moreover, 61 percent of all new chemical compounds that were present globally in the same time periods were found to be derived from natural products (Newman et al., 2003).

PROTECTIVE ROLE OF VARIOUS ETHNOPHARMACOLOGICAL DRUGS AGAINST TOXICITY OF VITAL ORGAN

Hepatotoxicity and ethnopharmacological medicines

The liver is an important body organ that primarily regulates the metabolism of exogenous as well as endogenous agents (Senthilkumar et al., 2014). It has a key role in detoxification as well as the eradication of drugs and their metabolites. Hepatic damage can be induced due to infection, alcohol consumption, medications, xenobiotics, malnutrition, and anemia (Mroueh et al., 2004). These factors promote reactive oxygen species (ROS) production which is considered as prime cause of hepatotoxicity (Sanchez-Valle et al., 2012). Reactive oxygen species are reported to instigate lipid peroxidation by oxidizing molecules which are present in the cellular membranes as well as tissues. Furthermore, excessive generation of ROS can induce oxidative stress (OS) which leads to inflammatory as well as apoptotic responses. Synthetic medicines that are employed against hepatic disorders have deleterious side effects therefore the use of traditional medicinal plants (Tab 1) is now becoming a global trend (Li et al., 2015).

Rhodiola imbricata, also named arctic or golden root, is a traditional herbal medicine used in Mongolia, Soviet Republics, China, and Tibet (Kelly, 2001). It possesses the ability to increase the level of antioxidant markers in the liver and is therefore designated as a hepatoprotective medicine (Senthilkumar et al., 2014). *Fufang Zhenzhu Tiaozhi*, a capsule made from the combination of eight traditional Chinese medicinal herbs is documented to exhibit a hepatoprotective effect against toxicity induced by the fatty liver (non-alcoholic) as well as type 2 diabetes mellitus (Bei et al., 2019; Wang et al, 2021). *Hippophae rhamnoides* L. also named as sea buckthorn is a deciduous shrub which belongs to the Elaeagnaceae family and is reported to be involved in nitrogen fixation [Fig 2., (Hou

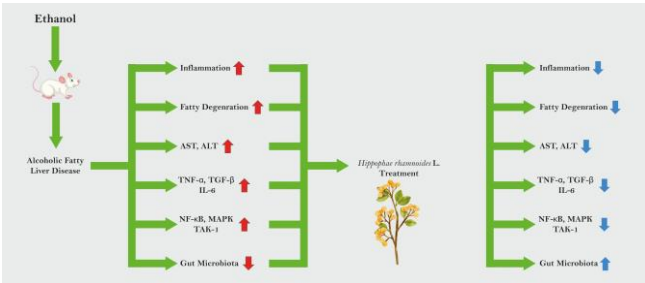


Fig 2. *Hippophae rhamnoides* mitigate ethanol induced fatty liver disorder.

et al., 2017)]. This plant has multiple medicinal as well as edible applications and it has been used in Europe and Asia for centuries (Kosman et al., 2009; Tian et al., 2020).

Zhao et al. (2022) used the extract of this plant as a stupendous hepatoprotective drug against liver injury induced by the accumulation of fats. It is documented that many natural remedies that improve liver function during various sorts of damage have the ability to modify intestinal flora while sea buckthorn alleviated the inflammation as well as fatty degeneration of liver cells induced by ethanol in mice. It also reconstructed the structure of gut microbiota which reverses the development of alcoholic fatty liver. Moreover, it attenuated Transforming growth factor-β-activated kinase 1-

Tab 1. Ethnopharmacological plants against hepatotoxicity

Plant	Common Name	Effect against Hepatotoxicity	Reference
<i>Citri Reticulatae Pericarpium</i>	Chenpi	It plays essential role in the treatment of multiple liver disorders and acts as an anti-inflammatory as well as antioxidative agent.	(Yu et al., 2018).
<i>Antrodia cinnamomea</i>	Antrodia cinnamomea	It is a medicinal fungus which is hosted by the trunks of <i>cinnamomum kanehirai</i> Hayata. It is reported to protect liver from fatty liver disorder (non-alcoholic) by reducing OS, inflammation as well as lipogenesis and promotes β-oxidation of fatty acid	(Lu et al., 2013; Cao et al., 2022)
<i>Dendrobium</i>	Orchid	It demonstrates hepatoprotective potential against CCl4-induced acute liver injury via regulating Nrf-2 signaling pathway as well as it enhances the metabolism of lipids and elevates the level of antioxidant enzymes.	(Li et al., 2019; Zhou et al., 2020; Huang et al., 2019; He et al., 2019)

induced (TAK1), Mitogen-activated protein kinases (MAPKs) as well as nuclear transcriptional factor NF-κB activation. These biochemical changes mediated by sea buckthorn ameliorated the ethanol-induced alcoholic fatty liver disease.

Renal toxicity and ethnopharmacological medicines

The kidney is an important organ with significant cellular complexity as well as functional diversity such as maintenance of composition, pressure, and volume of blood, as well as eradication of nitrogenous wastes (Little & McMahon 2012). Acute kidney injury (AKI) is a common problem linked with high levels of morbidity as well as death. According to previous

senegalensis is proven to attenuate nephrotoxicity induced by malarial parasites (Adetutu et al., 2015). *Phyllanthus niruri* is a widely used ethnopharmacological plant in South and Southeast Asia (Giribabu et al., 2017) and is commonly named a stone breaker or Chanca Piedra in Brazil which is used to cure renal as well as ureteric calculi (Calixto et al., 1998). Research demonstrates that *P. niruri* prevents stone formation in renal tissues by inhibiting the growth of urate crystals (Freitas et al., 2002) alternating the renal stone composition and making it more delicate as well as easily dissolvable (Barros et al., 2006). Furthermore, it induces relaxation of the urethra as well as diminishes the excretion of crystallization promoters such as calcium in the urine (Boim et al., 2010). This medicinal herb is an effective treatment for hemorrhagic cystitis as well as it

Tab 2. Traditional Chinese medicinal formulas used in the treatment of renal disorders

Formula	Herbs	Effect on Kidney	References
Liu-Wei-Di-Huang Wan	Rhizoma Rehmanniae Preparata; Fructus Corni; Rhizoma Dioscoreae; Rhizoma Alismatis; Cortex Moutan Radicis; Poria	Protect kidney against diabetic nephropathy (type 2 diabetes mellitus)	Hsu et al., 2014
Wuling San	Polyporus (<i>Polyporus umbellatus</i> Fries); Poria (<i>Poriacocos</i> Wolf); Alismatis rhizome (<i>Alisma orientale</i> Juz.); Cinnamomi cortex (<i>Cinnamomum cassia</i> J. Presl); <i>Atractylodis macrocephalae</i> rhizome	Increases urinary volume and reduced average body weight in patients suffering from nephritic syndrome. Ameliorate diabetic nephropathy induced renal edema. Anti-hyperuricemic as well as anti-inflammatory effects against hyperuricemia with kidney disfunction	Jin et al.,2012; Xiong et al., 2011; Yang et al., 2015
Mixture of <i>Astragalus membranaceus</i> and	<i>Astragalus membranaceus</i> ; <i>Salvia miltiorrhiza</i>	Relieve proteinuria, reduce mortality as well as improve renal function as a consequence of chronic kidney disease. Ameliorate kidney pathology as well as metabolism, restore	Hsieh et al., 2017; Huang et al., 2018;

Tab 3. Traditional medicinal plants to cure testicular toxicity.

Plant	Common Name	Effect	Reference
<i>Morinda officinalis</i>	Indian Mulberry	Improve sexual function of male mice. Protect human sperm DNA from oxidative stress	Wu et al., 2015
<i>Nigella sativa</i>	Black Cumin; Habbatus Sauda; Kalonji	Its oil can attenuate testicular toxicity and enhance sperm quality	Ping et al.,2014
<i>Moringa oleifera</i> Lam.	Drumstick tree	It can modulate the gene expressions related to Sertoli and spermatogonial cell. Enhances blood and intratesticular hormonal milieu.	Matic et al., 2018; Nayak et al., 2020
<i>Mucuna pruriens</i>	Magic velvet bean	Treat hypoactive sexual desire disorder and improve the sexual behaviors as well as improve functional proteins of testes.	Tangsriskakda et al., 2022
<i>Pogostemon cablin</i> (Blanco) Benth	Patchouli	Various extracts from the leaves of this plant can attenuate testicular toxicity via reducing OS, increasing sperm count, motility as well as viability.	Ijaz et al., 2022
<i>Taraxacum officinale</i> L.	Dandelion	It can reduce OS and inflammation meanwhile increasing the level of luteinizing hormone and testosterone.	Abdel-Magied et al., 2019
<i>Tamarindus indica</i> Linn.	Tamarind	It can treat diabetes induced testicular toxicity via increasing the level of serum insulin, sperm viability, sperm count and seminal vesicular fructose which is used by spermatozoa. Moreover, it attenuated OS and recovered antioxidant enzymes.	Maiti, 2017

literature, one out of every five adults and one out of every three children suffer from acute kidney injury (Susantitaphong et al., 2013). Various renal toxicants and infections are considered the primary causes of acute kidney injury (Barnett et al., 2019).

Khaya senegalensis commonly known as a dry zone mahogany is a medicinal plant used by Nupes of Nigeria as well as in other regions of Africa (Adebayo et al., 2003). *Khaya*

relieves diabetes mellitus-induced kidney damage by inhibiting OS, apoptosis, inflammation, and kidney proliferation (Boeira et al., 2011; Giribabu et al., 2017). Some other plants that are used against diabetic nephropathy include *Murraya koeingii* and *Brassica juncea* (Grover et al., 2003). Several traditional Chinese medicine formulas that consist of multiple types of herbs are widely used to treat kidney disorders (Tab 2).

Testicular toxicity and ethnopharmacological medicines

Testes are reproductive organs which are primarily responsible for reproduction and are present outside the human body (Seevagan et al., 2019). They perform endocrine as well as exocrine functions (Tiwana and Leslie, 2017). Toxicity of testicles is the primary cause of infertility and can be induced by multiple factors including nutritional, environmental, and hormonal imbalances (Dubey et al., 2018).

Cerely (*Apium graveolens* L.) is a widely used traditional folk medicine to treat multiple diseases like gastrointestinal disorders and rheumatism. (Maruyama et al., 2009). The seeds of this plant are used as a sedative, hypotensive, diuretic, and spasmolytic agent as well as to enhance fertility (Al-Asmari et al., 2017; Kooti et al., 2017). The oils of celery have the potential to reduce OS in testes and enhance the function of sperms. Moreover, it can increase the level of testosterone (Helal, 2014; Khiabani, 2014; Madkour, 2014; Shalaby and El-Zorba, 2010). Cistanche (*Cistanche Hoffmy*) is a traditional plant which is used as a therapeutic approach for testicular dysfunction and is reported to enhance the sexual function of males via increasing testosterone production (Tab 3). This plant is commonly found in the semi-arid regions of India, Mongolia, and China (Wang et al., 2016). Cistanche upregulates steroidogenic enzymes in order to attenuate testicular toxicity (Jiang et al., 2016). *Urtica dioica* is a folk medicine which is documented to increase sperm count and motility. It also helps in maintaining the normal diameter of seminiferous tubules and sperm cell morphology as well as increasing the testosterone level and quality of spermatozoa (Jalili et al., 2014).

cardiovascular disorders are the major cause of death worldwide (WHO, 2019). Cardiac Muscle damage, electrophysiological disturbances, and vascular endothelial dysfunction are some of the factors that can contribute to cardiovascular toxicity (Singh., 2016). Cardiotoxicity is induced by various drugs including anticancers such as chemotherapeutics as well as different kinds of anti-depressants (McGowan et al., 2017). Furthermore, air pollution (Rao, 2018) and plastic exposure (Posnack, 2021) as well as excessive consumption of alcohol can lead to severe cardiovascular disorders including cardiac arrhythmias and dilated cardiomyopathy (DCM) (Xi et al., 2017). These abnormalities can disrupt blood circulation as well as continuous flow. Moreover, inflammation as well as OS play a central pathogenic role inducing cardiovascular toxicity (Kovacic and Thurn, 2005; Juni et al., 2013).

Sweet marjoram (*Origanum majorana* L.) is a native plant to the Mediterranean region and planted in many other countries of Europe, North Africa, and Asia (Bina and Rahimi, 2017). It is effective against thrombocytosis, granulocytosis, and erythrocytosis as well as against increased heart weight, OS, and myocardial infarction (Ramadan et al., 2013). *Ginkgo biloba* L., a deciduous plant of the genus Ginkgo usually known as a living fossil (Hassan et al., 2020), which is extensively used for various purposes such as medicine, ornamental, food, material, and greening (Tab 4). Extract of *Ginkgo biloba* L. can be used against myocardial infarction as it can diminish the deposition of cholesterol in peripheral tissues, counter atherosclerosis production, and prevent damage to vascular endothelial cells (Chen et al., 2014).

Tab 4. Ethnopharmacological plants against cardiotoxicity.

Plant	Common Name	Effect against cardiotoxicity	Reference
<i>Cnidium monnieri</i> (L.)	Monnier's snowparsley	It can reduce systolic blood pressure (Ogawa et al., 2007) and demonstrates strong vaso-relaxing effect. Moreover, it alleviates cardiac hypertrophy as result of renovascular hypertension via inhibiting OS, lipid metabolism and NF-kB in cardiac tissues.	Chiou et al., 2001; Chen et al., 2011
<i>Saussurea lappa</i>	Costus	It attenuated Ehrlich Solid Tumour (a tumour that promotes breast cancer) prompted cardiotoxicity via improved the levels of sodium and high-density lipoproteins. Furthermore, it enhances lipid profiles and electrolytes in cardiac tissues and also increased apoptosis against cancerous cells.	Elgharabawy et al., 2021
<i>Glycyrrhiza glabra</i>	Licorice	It mitigated Doxorubicin induced cardiotoxicity through regulating the metabolism and homeostasis of lipids, diminishing OS, sustaining the functions of mitochondria and prevented cardiac heteropathy.	Upadhyay et al., 2020
<i>Platycodon grandiflorum</i>	Baloon flower or Chinese bellflower	It is reported to cure anthracycline (a chemotherapeutic drug applied against breast cancer) induced cardiotoxicity. It protects cardiac tissues from systolic dysfunction as well as myocardial injury.	Hao et al., 2020

Cardiovascular diseases and ethnopharmacological medicines

The heart is a vital organ made up of cardiac muscles, involved in the distribution of oxygenated blood throughout the body. It carries oxygenated blood to the body's organs while pumping deoxygenated blood toward the pulmonary system (Kenny et al., 2011). According to a report published by WHO,

Ethnopharmacological drugs and their therapeutic action against lung toxicity

Lungs are considered important organs of the respiratory system which are responsible for the exchange of gases between blood and its environment (Lutfi, 2017). Lungs divide into many portions, which are further segmented into more than 300 million alveoli primary sites for gaseous exchange (Chaudhry &

Bordoni 2022). Many harmful reactions take place inside the lungs which are responsible for cancer, asthma, and chronic obstructive pulmonary disease, because of exposure of the lungs to different toxicants such as cigarette smoke, nitrogen oxides,

well as its paste is applied on the skin of goat, chicken and cow for wounds treatment (Selvaraju et al.,2011).

Licorice is a root of *Glycyrrhiza* plant, a member of the

Tab 5. Ethnopharmacological plants against Pulmonotoxicity.

Plant	Common Name	Effect against Pulmonotoxicity	Reference
<i>Selaginella doederleinii</i>	Spikemoss or Club moss	It protects lungs from toxicity induced by lungs cancer via prompting mitochondrial pathways and promoting apoptosis of cancerous cells.	Sui et al., 2016
<i>Abutilon pannosum</i>	Ragged Mellow or Peeli Boti (Urdu)	It protected the lungs toxicity via reducing OS, inflammation, apoptosis and improved antioxidant enzymes of lungs.	Khalil et al., 2020
<i>Zataria multiflora</i>	Avishane-shirazi (Persian)	It mitigates cisplatin induced lung damage by increasing the activity of the antioxidant defense system, scavenging the ROS that induce lipid peroxidation as well as via quenching free radicals.	Habibi et al., 2020

industrial contaminants, ozone, and many other substances (Kovacac & Somanathan 2009).

Ziziphora tenuior L. is a traditional medicinal plant which is enriched with various flavonoids, polyphenolic, and phenolic compounds usually found from Southwest Asia to Eastern Europe (Mehmood et al., 2010). In traditional medicine (Tab 5), it is broadly used as herbal tea to cure asthma and gastrointestinal disorders (Pirbalouti et al., 2010). The extract of *Z. tenuior* exhibits pulmonary protective function against chlorpyrifos-induced lung toxicity owing to its free radical scavenging action as well as anti-inflammatory properties (Kianpour et al., 2021). *Andrographis paniculata* (Burm.f.) Nees is a medicinal plant and is a member of the family Acanthaceae. It is well known for its curative potential against respiratory tract infections, sore throat, diarrhea, and liver disorders in Southeast Asian countries such as India and China (Hossain et al., 2014). It has the ability to attenuate cisplatin-induced lung damage by enhancing the activity of the antioxidant defense system, and scavenging free radicals that induce liver peroxidation and peroxidative damage (Habibi et al., 2018).

THERAPEUTIC ACTION OF ETHNOPHARMACOLOGICAL DRUGS AGAINST VITAL ORGAN TOXICITY IN ANIMALS

Multiple ethnopharmacological medicines are applied to cure various disorders in animals. *Herniaria hirsuta* L. (hairy rupturewort) is a plant of the genus *Herniaria* (Caryophyllaceae) which is commonly reported in North Africa, Asia as well as Europe. It possesses the ability to lower cholesterol levels in the bile of dogs. Furthermore, it has the ability to dissolve existing gallstones and prevent the formation of new gallstones (Dooren et al., 2015). *Acalypha indica* is an ethnopharmacological plant which is usually found in Africa and Asia (Zahidin et al., 2017). It is applied against various disorders in animals such as anthrax in cattle as well as camel (Giday and Teklehaymanot 2013), bovine mastitis (Mubarack et al., 2012), constipation, and maggot wound (Pandit, 2010), as

family Leguminosae, and used as a traditional medicine since bygone times (Shibata 2000). It is used as a feed additive, and its constituents can elevate the production efficiency of broilers, rabbits, sows, and pigeons and keep their intestine healthy (Ibrahim et al., 2020). Moreover, it improves immunity along with the meat quality of animals (Luo et al., 2019). Chamomile (*Maricaria recutita* L.) is a popular traditional medicine that is used against gastrointestinal disorders including diarrhea (Alanís et al., 2005).

CONCLUSION

In conclusion, ethnopharmacology has emerged as a promising field in mitigating vital organ toxicity in both humans and livestock. The use of natural products with medicinal properties has gained widespread attention in recent years due to their potential therapeutic benefits and minimal side effects. Ethnopharmacology has the potential to offer safe and effective alternatives for the prevention and treatment of vital organ toxicity, improving the health and well-being of humans and livestock alike. However, it is important to note that further studies are needed to fully understand the pharmacological mechanisms and potential risks associated with these natural remedies.

REFERENCES

Abdel-Magied N, SM Abdel-Fattah & AA Elkady, 2019. Differential effect of *Taraxacum officinale* L.(dandelion) root extract on hepatic and testicular tissues of rats exposed to ionizing radiation. Molecular Biology Reports 46:4893-4907.

Adebayo JO, MT Yakubu, EC Egwim, VB Owoyele & BU Enaibe, 2003. Effect of ethanolic extract of Khaya senegalensis on some biochemical parameters of rat kidney. Journal of Ethnopharmacology 88:69-72.

Adekomi AD, 2020. Madagascar periwinkle (*Catharanthus roseus*) enhances kidney and liver functions in Wistar rats. European Journal of Anatomy 14:111-119.

Adetutu A, OS Olorunnisola & K Iyanda, 2015. Protection of renal function by four selected plant extracts during *Plasmodium berghei* infection. Functional Foods in Health and Disease 5:339-349.

Alanis AD, F Calzada, JA Cervantes, J Torres & GM Ceballos, 2005. Antibacterial properties of some plants used in Mexican traditional medicine

- p>for the treatment of gastrointestinal disorders. Journal of Ethnopharmacology 100:153-157.
- Al-Asmari AK, MT Athar & SG Kadasah, 2017. An updated phytopharmacological review on medicinal plant of Arab region: *Apium graveolens* linn. Pharmacognosy reviews 11:13.
- Barnett LMA & BS Cummings, 2019, March. Cellular and molecular mechanisms of kidney toxicity. In Seminars in nephrology 39(2):141-151.
- Barros ME, R Lima, LP Mercuri, JR Matos, N Schor & MA Boim, 2006. Effect of extract of *Phyllanthus niruri* on crystal deposition in experimental urolithiasis. Urological Research 34:351-357.
- Bei W, Y Wang, J Chen, J Zhang, L Wang, Z Gu, Y Hu, Y Huang, W Xu, Z Lei & J Cai, 2019. Chinese medicine FTZ recipe protects against high-glucose-induced beta cell injury through alleviating oxidative stress. Evidence-Based Complementary and Alternative Medicine 7828209.
- Bina F & R Rahimi, 2017. Sweet marjoram: a review of ethnopharmacology, phytochemistry, and biological activities. Journal of evidence-based complementary & alternative medicine 22:175-185.
- Boeira VT, CE Leite, Jr AA Santos, MI Edelweiss, JB Calixto, MM Campos & FB Morrone, 2011. Effects of the hydroalcoholic extract of *Phyllanthus niruri* and its isolated compounds on cyclophosphamide-induced hemorrhagic cystitis in mouse. Naunyn-Schmiedeberg's archives of pharmacology 384:265-275.
- Boim MA, IP Heilberg, N Schor, 2010. *Phyllanthus niruri* as a promising alternative treatment for nephrolithiasis. International Brazilian Journal of Urology 36:657-664.
- Bruhn JG & B Holmstedt, 1981. Ethnopharmacology, Objectives, Principles and Perspectives. In: J.L. Beal and E. Reinhard (Eds.) Natural Products OS Medicinal Agents, Hippokrates Verlag, Stuttgart, pp. 405-430.
- Calixto JB, AR Santos, VC Filho & RA Yunes, 1998. A review of the plants of the genus *Phyllanthus*: their chemistry, pharmacology, and therapeutic potential. Medicinal research reviews 18:225-258.
- Cao YN, SS Yue, AY Wang, L Xu, YT Hu, X Qiao, TY Wu, M Ye, YC Wu & R Qi, 2022. *Antrodia cinnamomea* and its compound dehydroeburicoic acid attenuate nonalcoholic fatty liver disease by upregulating ALDH2 activity. Journal of Ethnopharmacology 292:115146.
- Chaudhry R & B Bordoni, Anatomy, 2022. Thorax, Lungs. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan-. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK470197/>
- Chen M, J Su, Y Zhang, S Chen & G Lv, 2014. A comparative study on effects of *Ginkgo biloba* extract and *Ginkgo* flavonoid on Lipid Metabolism in SD Rats with hyperlipidemia. Chinese Journal of New Drugs 23:833-838.
- Chen R, J Xue & ML Xie, 2011. Reduction of isoprenaline-induced myocardial TGF- β 1 expression and fibrosis in osthole-treated mice. Toxicology and applied pharmacology 256: 168-173.
- Chiou WF, YL Huang, CF Chen & CC Chen, 2001. Vasorelaxing effect of coumarins from *Cnidium monnieri* on rabbit corpus cavernosum. Planta medica 67:282-284.
- Ping CN, NH Hashim & DS Hasan Adli, 2014. Effects of *Nigella sativa* (*Habbatus sauda*) oil and nicotine chronic treatments on sperm parameters and testis histological features of rats. Evidence-Based Complementary and Alternative Medicine 2014: 218293.
- Dubey S, M Shri, A Gupta, V Rani & D Chakrabarty, 2018. Toxicity and detoxification of heavy metals during plant growth and metabolism. Environmental Chemistry Letters 16:1169-1192.
- Efron DH, B Holmstedt & NS Kline. 1967. Ethnopharmacological search for psychoactive drugs. US Department of Health, Education and Welfare, Government Printing Office, Washington DC, USA. Publ 1645.
- Elgharabawy RM, I El Tantawy El Sayed, N Abd-Allah Rezk & E Tousson, 2021. Therapeutic impact of costus (*Saussurea lappa*) against Ehrlich solid tumor-induced cardiac toxicity and DNA damage in female mice. Frontiers in Pharmacology 12:708785.
- Fabricant DS & NR Farnsworth, 2001. The value of plants used in traditional medicine for drug discovery. Environmental health perspectives, 109, 1:69-75.
- Freitas AM, N Schor, & MA Boim, 2002. The effect of *Phyllanthus niruri* on urinary inhibitors of calcium oxalate crystallization and other factors associated with renal stone formation. BJU international 89:829-834.
- Giday M & T Teklehaymanot, 2013. Ethnobotanical study of plants used in management of livestock health problems by Afar people of Ada'ar District, Afar Regional State, Ethiopia. Journal of Ethnobiology and Ethnomedicine 9:1-10.
- Giribabu N, K Karim, EK Kilari & N Salleh, 2017. *Phyllanthus niruri* leaves aqueous extract improves kidney functions, ameliorates kidney oxidative stress, inflammation, fibrosis and apoptosis and enhances kidney cell proliferation in adult male rats with diabetes mellitus. Journal of ethnopharmacology 205:123-137.
- Grover JK, SP Yadav & V Vats, 2003. Effect of feeding *Murraya koeingii* and *Brassica juncea* diet kidney functions and glucose levels in streptozotocin diabetic mice. Journal of ethnopharmacology 85:1-5.
- Habibi E, M Shokrzadeh, A Ahmadi, A Chabra, F Naghshvar, H Haghi-Aminjan & F Salehi, 2020. Pulmonoprotective action of *Zataria multiflora* ethanolic extract on cyclophosphamide-induced oxidative lung toxicity in mice. Chinese journal of integrative medicine 26:754-761.
- Han C, YH Jiang, W Li & Y Liu, 2021 *Astragalus membranaceus* and *Salvia miltiorrhiza* ameliorates cyclosporin A-induced chronic nephrotoxicity through the "gut-kidney axis". Journal of Ethnopharmacology 6:269:113768.
- Hao W, Y Shi, Y Qin, C Sun, L Chen, C Wu, Y Bao & S Liu, 2020. *Platycodon grandiflorum* protects against anthracycline-induced cardiotoxicity in early breast cancer patients. Integrative Cancer Therapies 19:1534735420945017.
- Harvey AL, 2008. Natural products in drug discovery. Drug discovery today 13(19-20):894-901.
- Hassan I, WN Wan Ibrahim, FM Yusuf, SA Ahmad & S Ahmad, 2020. Biochemical Constituent of *Ginkgo biloba* (Seed) 80% Methanol Extract Inhibits Cholinesterase Enzymes in Javanese Medaka (*Oryzias javanicus*) Model. Journal of toxicology 2020:8815313.
- He K, D Zhang, X Li, R Liu, J Huang & M Liu, 2019. Inhibitory effect of *Dendrobium nobile* wall breaking powder on the growth of human hepatoma cells HepG2 in nude mice. Chinese Pharmaceutical Journal 54:1865-1870.
- Helal MA, 2014. Celery oil modulates DEHP-induced reproductive toxicity in male rats. Reproductive biology 14:182-189.
- Hossain MD, Z Urbi, A Sule & KM Rahman, 2014. *Andrographis paniculata* (Burm. f.) Wall. ex Nees: a review of ethnobotany, phytochemistry, and pharmacology. The Scientific World Journal 2014:274905.
- Hou D, D Wang, X Ma, W Chen, S Guo & H Guan, 2017. Effects of total flavonoids of sea buckthorn (*Hippophae rhamnoides* L.) on cytotoxicity of NK92-MI cells. International journal of immunopathology and pharmacology 30:353-361.
- Hsieh CF, HC Chang, SL Huang, CL Chen, WT Chen & CC Yang, 2017. Prescribed renoprotective Chinese herbal medicines were associated with a lower risk of all-cause and disease-specific mortality among patients with chronic kidney disease: a population-based follow-up study in taiwan. Evidence-Based Complementary and Alternative Medicine 2017: 5632195.
- Hsu PC, YT Tsai, JN Lai, CT Wu, SK Lin & CY Huang, 2014. Integrating traditional Chinese medicine healthcare into diabetes care by reducing the risk of developing kidney failure among type 2 diabetic patients: a population-based case control study. Journal of ethnopharmacology 156:358-364.
- Huang KC, YC Su, MF Sun & ST Huang, 2018. Chinese herbal medicine improves the long-term survival rate of patients with chronic kidney disease in Taiwan: a nationwide retrospective population-based cohort study. Frontiers in Pharmacology 9:1117.
- Huang S, Q Wu, H Liu, H Ling, Y He, C Wang, Z Wang, Y Lu & Y Lu, 2019. Alkaloids of *dendrobium nobile* lindl. Altered hepatic lipid homeostasis via regulation of bile acids. Journal of ethnopharmacology 241:111976.
- Ibrahim D, AH Sewid, AH Arisha, AH Abd El-Fattah, AM Abdelaziz, OA Al-Jabr & AT Kishawy, 2020. Influence of *Glycyrrhiza glabra* extract on growth, gene expression of gut integrity, and *Campylobacter jejuni* colonization in broiler chickens. Frontiers in Veterinary Science 7:612063.
- Ijaz MU, A Rauf, S Mustafa, H Ahmed, A Ashraf, K Al-Ghanim, SS Mruthinti, & S Mahboob, 2022. *Pachypodol* attenuates Perfluorooctane sulphonate-

- p induced testicular damage by reducing oxidative stress.
- Saudi Journal of Biological Sciences*
- 29:1380-1385.
- Jalili C, MR Salahshoor & A Naseri, 2014. Protective effect of *Urtica dioica* L against nicotine-induced damage on sperm parameters, testosterone and testis tissue in mice. *Iranian journal of reproductive medicine* 12:401.
- Jiang Z, J Wang, X Li & X Zhang, 2016. Echinacoside and *Cistanche tubulosa* (Schenk) R. wight ameliorate bisphenol A-induced testicular and sperm damage in rats through gonad axis regulated steroidogenic enzymes. *Journal of ethnopharmacology* 193:321-328.
- Jiang, W Li & Y Liu, 2021. *Astragalus membranaceus* and *Salvia miltiorrhiza* ameliorates cyclosporin A-induced chronic nephrotoxicity through the “gut-kidney axis”. *Journal of ethnopharmacology* 269:113768.
- Jin R, R Yu, H Gao, CX Yang, F Fang & JN Wang, 2012. Comparative study of Wuling powder and Wuling decoction for nephrotic syndrome patients of water-damp collecting internally syndrome. *Journal of Traditional Chinese Medicine* 53:572-573.
- Kelly GS, 2001. *Rhodiola rosea*: a possible plant adaptogen. *Alternative Medicine Review* 6:293-302.
- Kenny WL, JH Wilmore & DL Costill, 2011. Cardiovascular System and its Control. In: *Physiology of Sport and Exercise*, 5th ed. Human Kinetics, pp:140-150.
- Khalil I, M Ghani, MR Khan & F Akbar, 2020. Evaluation of biological activities and in vivo amelioration of CCl4 induced toxicity in lung and kidney with *Abutilon pannosum* (G. Forst.) Schltdl. in rat. *Journal of ethnopharmacology*, 249:112395.
- Khamkar AD, VM Motghare, R Deshpande. 2015. Ethnopharmacology—a novel approach for drug discovery. *Indian Journal of Pharmacology* 2(4):222-5.
- Kianpour F, M Mohseni, M Beigmohamadi, A Yazdinezhad, A Ramazani, MJ Hosseini & A Sharafi, 2021. The protective effects of *Ziziphora tenuior* L. against chlorpyrifos induced toxicity: Involvement of inflammatory and cell death signaling pathways. *Journal of ethnopharmacology* 272:113959.
- Kooti W, M Moradi, K Peyro, M Sharghi, F Alamiri, M Azami, M Firoozbakht & M Ghafourian, 2017. The effect of celery (*Apium graveolens* L.) on fertility: A systematic review. *Journal of Complementary and Integrative Medicine* 15:20160141.
- Kosman VM, NM Faustova, ON Pozharitskaia, AN Shikov, B Galambozi, & VG Makarov, 2009. Phytochemical analysis of *Hippophae rhamnoides* L. fruits from Russian varieties cultivated in Finland and food products containing them. *Voprosy Pitaniia* 78:38-42.
- Kovacic P & LA Thurn, 2005. Cardiovascular toxicity from the perspective of oxidative stress, electron transfer, and prevention by antioxidants. *Current vascular pharmacology* 3:107-117.
- Kovacic P & R Somanathan, 2009. Pulmonary toxicity and environmental contamination: radicals, electron transfer, and protection by antioxidants. *Reviews of Environmental Contamination and Toxicology* 201:41-69.
- Li S, HY Tan, N Wang, ZJ Zhang, L Lao, CW Wong & Y Feng, 2015. The role of oxidative stress and antioxidants in liver diseases. *International journal of molecular sciences*, 16:26087-26124.
- Li S, J Zhou, S Xu, J Li, J Liu, Y Lu, J Shi, S Zhou & Q Wu, 2019. Induction of Nrf2 pathway by *Dendrobium nobile* Lindl. Alkaloids protects against carbon tetrachloride induced acute liver injury. *Biomedicine & Pharmacotherapy* 117:109073.
- Little MH & AP McMahon, 2012. Mammalian kidney development: principles, progress, and projections. *Cold Spring Harbor perspectives in biology* 4:a008300.
- Lu MC, M El-Shazly, TY Wu, YC Du, TT Chang, CF Chen, YM Hsu, KH Lai, CP Chiu, FR Chang & YC Wu, 2013. Recent research and development of *Antrodia cinnamomea*. *Pharmacology & therapeutics* 139:124-156.
- Lutfi MF, 2017. The physiological basis and clinical significance of lung volume measurements. *Multidisciplinary respiratory medicine* 12:1-12.
- Madkour NK, 2014. Beneficial role of celery oil in lowering the di (2-ethylhexyl) phthalate-induced testicular damage. *Toxicology and Industrial Health* 30:861-872.
- Maiti R, 2017. Diabetes-induced testicular dysfunction correction by hydromethanolic extract of *Tamarindus indica* Linn. seed in male albino rat. *International Journal of Green Pharmacy (IJGP)* 11: S790-S796.
- Maruyama T, A Abbaskhan, MI Choudhary, Y Tsuda, Y Goda, M Farille & JP Reduron, 2009. Botanical Origin of Indian Celery Seed (Fruit). *Journal of natural medicines* 63:248-253.
- Matic I, A Guidi, M Kenzo, M Mattei & A Galgani, 2018. Investigation of medicinal plants traditionally used as dietary supplements: A review on *Moringa oleifera*. *Journal of public health in Africa* 9:841.
- McGowan JV, R Chung, A Maulik, I Piotrowska, JM Walker & DM Yellon, 2017. Anthracycline chemotherapy and cardiotoxicity. *Cardiovascular drugs and therapy* 31:63-75.
- Mehmood R, M Imran, A Malik & RB Tareen, 2010. Ziziphorins A and B. New Flavonoids from *Ziziphora tenuior*. *Zeitschrift für Naturforschung B* 65:1397-1400.
- Mroueh M, Y Saab & R Rizkallah, 2004. Hepatoprotective activity of *Centaurium erythraea* on acetaminophen-induced hepatotoxicity in rats. *Phytotherapy Research: An International Journal Devoted to Pharmacological and Toxicological Evaluation of Natural Product Derivatives* 18:431-433.
- Mubarack HM, A Doss, SP Anand, R Venkataswamy, M Vijayasanthi, 2012. Survey of ethnoveterinary medicinal plants in Coimbatore region, Tamilnadu, South India—a special reference to Bovine Mastitis. *South Asian Journal of Biological Sciences* 2:31-36.
- Nayak G, A Rao, P Mullick, S Mutalik, SG Kalthur, SK Adiga & G Kalthur, 2020. Ethanolic extract of *Moringa oleifera* leaves alleviate cyclophosphamide-induced testicular toxicity by improving endocrine function and modulating cell specific gene expression in mouse testis. *Journal of Ethnopharmacology* 259:112922.
- Newman DJ, GM Cragg & KM Snader, 2003. Natural products as sources of new drugs over the period 1981–2002. *Journal of natural products* 66:1022-1037.
- Pirbalouti AG, F Malekpour, S Enteshari, M Yousefi, H Momtaz & B Hamed, 2010. Antibacterial activity of some folklore medicinal plants used by Bakhtiari tribal in Southwest Iran. *International Journal of Biology* 2:55.
- Posnack NG, 2021. Plastics and cardiovascular disease. *Nature Reviews Cardiology* 18:69-70.
- Ramadan G, NM El-Beih, NM Arafa & MM Zahra, 2013. Preventive effects of Egyptian sweet marjoram (*Origanum majorana* L.) leaves on haematological changes and cardiotoxicity in isoproterenol-treated albino rats. *Cardiovascular toxicology* 13:100-109.
- Rivier L & JG Bruhn, 1979. Editorial. *Journal of Ethnopharmacology* 1:1.
- Sánchez-Valle V, NC Chavez-Tapia, M Uribe & N Méndez-Sánchez, 2012. Role of oxidative stress and molecular changes in liver fibrosis: a review. *Current medicinal chemistry* 19:4850-4860.
- Seevagan T, S Hulligan, J Phull & OM Aboumarzouk, 2019. Testes structure and function. In: *Blandy's Urology*. Aboumarzouk om (ed.), John Wiley & Sons Ltd., Philadelphia, pp:729-739.
- Senthilkumar R, R Chandran & T Parimelazhagan, 2014. Hepatoprotective effect of *Rhodiola imbricata* rhizome against paracetamol-induced liver toxicity in rats. *Saudi journal of biological sciences* 21:409-416.
- Shalaby MA & HY El-Zorba, 2010. Protective effect of celery oil, vitamin e and their combination against testicular toxicity in male rats. *Global veterinaria* 5:122-128.
- Shibata S, 2000. A drug over the millennia: pharmacognosy, chemistry, and pharmacology of licorice. *Yakugaku Zasshi* 120:849-862 (in Japanese)
- Sui Y, S Li, P Shi, Y Wu, Y Li, W Chen, L Huang, H Yao & X Lin, 2016. Ethyl acetate extract from *Selaginella doederleinii* Hieron inhibits the growth of human lung cancer cells A549 via caspase-dependent apoptosis pathway. *Journal of ethnopharmacology* 190:261-271.
- Susantitaphong P, DN Cruz, J Cerda, M Abulfaraj, F Alqahtani, I Koulouridis & BL Jaber, 2013. World incidence of AKI: a meta-analysis. *Clinical Journal of the American Society of Nephrology* 8:1482-1493.
- Tangrisakda N, T Kamollerd, C Taoto, S Bunsueb, C Chaimontri, P Choowong-In, N Lapyuneyong, AT Wu, W Thukhammee & J Wattanathorn, S Arun, 2022. Seed extract of Thai *Mucuna pruriens* (L.) DC. var. pruriens

- enhances sexual performance and improves male reproductive damages in ethanol-induced rats. *Journal of ethnopharmacology* 28: 292:115219.
- Tian R, H Wang, Y Xiao, P Hu, R Du, X Shi, Z Wang & Y Xie, 2020. Fabrication of nanosuspensions to improve the oral bioavailability of total flavones from *Hippophae rhamnoides* L. and their comparison with an inclusion complex. *AAPS PharmSciTech* 21:249.
- Tiwana MS & SW Leslie. 2022. Anatomy, Abdomen and Pelvis: Testicle. In: StatPearls [Internet]. Treasure Island (FL), StatPearls Publishing.
- UNESCO. 2013. Report of the International Bioethics Committee on Traditional Medicine Systems and their ethical implications. SHS/EGC/IBC-19/12/3 Rev. Paris, 8 February.
- Upadhyay S, AK Mantha, & M Dhiman, 2020. *Glycyrrhiza glabra* (Licorice) root extract attenuates doxorubicin-induced cardiotoxicity via alleviating oxidative stress and stabilizing the cardiac health in H9c2 cardiomyocytes. *Journal of ethnopharmacology* 258:112690
- van Dooren I, MEA Faouzi, K Foubert, M Theunis, L Pieters, Y Cherrah & S Apers, 2015. Cholesterol lowering effect in the gall bladder of dogs by a standardized infusion of *Herniaria hirsuta* L. *Journal of ethnopharmacology* 169:69-75.
- Wang T, C Chen, M Yang, B Deng, GM Kirby & X Zhang, 2016. *Cistanche tubulosa* ethanol extract mediates rat sex hormone levels by induction of testicular steroidogenic enzymes. *Pharmaceutical Biology* 54:481-487.
- Wu ZQ, DL Chen, FH Lin, L Lin, O Shuai, JY Wang, LK Qi & P Zhang, 2015. Effect of bajijiasu isolated from *Morinda officinalis* FC how on sexual function in male mice and its antioxidant protection of human sperm. *Journal of Ethnopharmacology* 164:283-292.
- Xi B, SP Veeranki, M Zhao, C Ma, Y Yan & J Mi, 2017. Relationship of alcohol consumption to all cause, cardiovascular, and cancer-related mortality in U.S. adults. *Journal of the American College of Cardiology* 70:913–22.
- Xiong KW, SG Lin, L Zhong, F Wu & XH Yan, 2011. Clinical observation of Wuling San in the treatment of early diabetic nephropathy edema. *International Journal of Clinical and Experimental Medicine* 10:1023–1024.
- Yang Y, DM Zhang, JH Liu, LS Hu, QC Xue, XQ Ding & LD Kong, 2015. Wuling San protects kidney dysfunction by inhibiting renal TLR4/MyD88 signaling and NLRP3 inflammasome activation in high fructose-induced hyperuricemic mice. *Journal of Ethnopharmacology* 169:49-59.
- Yu X, S Sun, Y Guo, Y Liu, D Yang, G Li & S Lü, 2018. *Citri Reticulatae pericarpium* (Chenpi): Botany, ethnopharmacology, phytochemistry, and pharmacology of a frequently used traditional Chinese medicine. *Journal of Ethnopharmacology* 220:265-282.
- Zahidin NS, S Saidin, RM Zulkifli, R. II Muhamad, H Ya'akob & H Nur, 2017. A review of *Acalypha indica* L.(Euphorbiaceae) as traditional medicinal plant and its therapeutic potential. *Journal of ethnopharmacology* 207:146-173.
- Zhao H, L Kong, M Shao, J Liu, C Sun, C Li, Y Wang, X Chai, Y Wang, Y Zhang & X Li, 2022. Protective effect of flavonoids extract of *Hippophae rhamnoides* L. on alcoholic fatty liver disease through regulating intestinal flora and inhibiting TAK1/p38MAPK/p65NF-κB pathway. *Journal of Ethnopharmacology* 292:115225
- Zhou J, Y Zhang, S Li, Q Zhou, Y Lu, J Shi, J Liu, Q Wu & S Zhou, 2020. *Dendrobium nobile* Lindl. alkaloids-mediated protection against CCl4-induced liver mitochondrial oxidative damage is dependent on the activation of Nrf2 signaling pathway. *Biomedicine and Pharmacotherapy* 129:110351.