



## PHARMACOLOGICAL UPDATES ON POTENTIAL PHYTOCONSTITUENTS OF GENUS *ZIZYPHUS*

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### ABSTRACT:

The popularity of herbal medicine enhance day by day because of its natural origin and lesser side effects. Nature has been a source of medicinal agents for thousands of year and an impressive number of modern drug have been isolated from natural sources, many based on their use in traditional medicine. Plants from the genus *Zizyphus* have been used in traditional medicine by many cultures. Flavonoids, phenolic compounds triterpenic acids and polysaccharides constituents have been reported as the major phyto-constituents of the *Zizyphus species*. This genus is represented by 100 species throughout the world. This review summarizes the morphology, traditional and folklore uses, phyto-chemical and pharmacological reports of the prominent species of the genus *Zizyphus* (*Z. jujube*, *Z. nummularia* & *Z. spina-christi*). Various virgin areas of research on the species of this genus have been highlighted with a view to explore, isolate and identify the medicinally important phyto-constituents which could be utilized as potent agent against many ailments and also as a substitute for synthetic therapeutic molecules and antibiotics having side effects.

**KEYWORDS:** *Zizyphus* (*Z. jujube*, *Z. nummularia* & *Z. spina-christi*), Ethno-pharmacology, Phyto-constituents, Pharmacological.

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## INTRODUCTION

Medicinal plants contribute a lot in the health sector, they are of great worth to the health of individuals as well as to the communities also<sup>1</sup>. India is well known as the "Emporium of Medicinal Plants". Due to these medicinal plants, the demand of medicinal plants has increased numerous folds. Various species of *Zizyphus* have medicinal significance and it is widely used in India, China and Japan<sup>2</sup>.

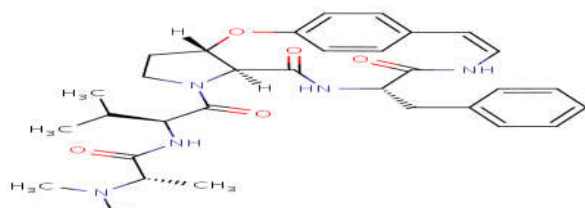


Fig 1 Mauritine-A

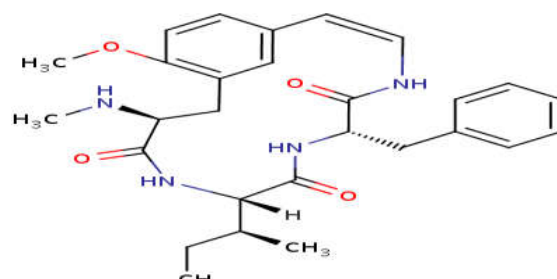


Fig 2: Mucronine-D



Fig 3: Nummularine-D

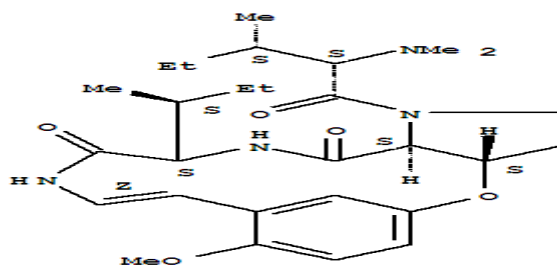


Fig 4: Sativanine

Saponins are one of the important constituents present in the seed and leaves of the *Z. jujube*<sup>4-6</sup>. Some of the

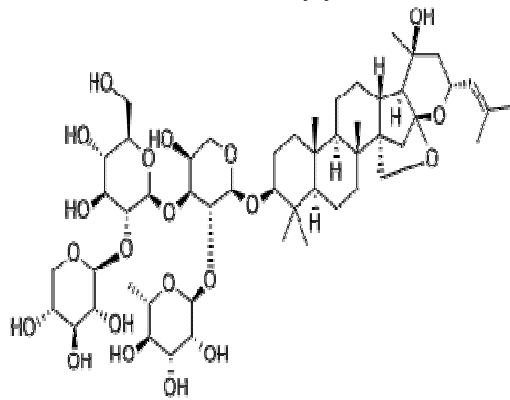


Fig 5: Jujubosides -B

saponins isolated from the seeds of *Z. jujuba* include:

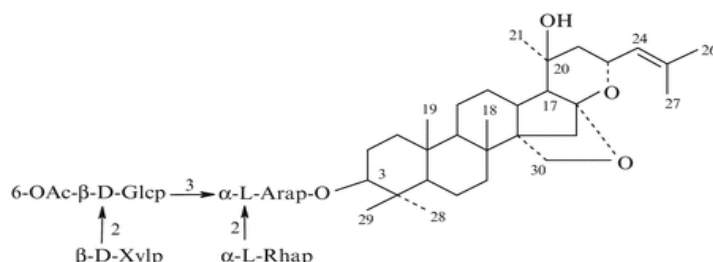


Fig 6: Acetyljujuboside B

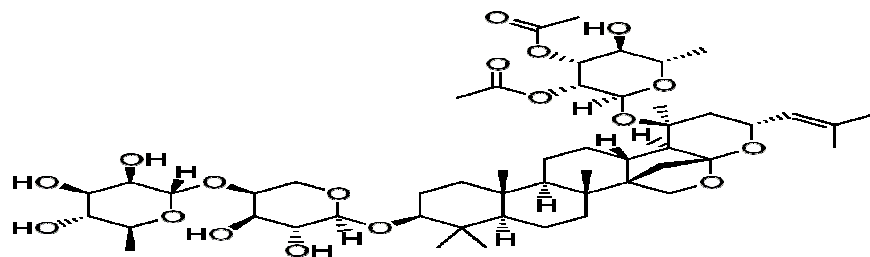


Fig 7: Ziziphin

Glycosides are also important constituent present in seed of *Z.jujube*. Some of the important glycosides are as follows: soyasapogenol B-3-O- $\alpha$ -L-rhamnopyranosyl (1 $\rightarrow$ 2)- $\beta$ -D-glucopyranosyl (1 $\rightarrow$ 4)- $\beta$ -D-glucuronopyranoside; juzirine, 6'''-feruloylspinosin (5-Hydroxy-6-[2-O-[6-O-[3-(4-hydroxy-3-methoxyphenyl)-1-oxo-2-propen-1-yl]-

$\beta$ -D-glucopyranosyl]- $\beta$ -D-glucopyranosyl]-2-(4-hydroxyphenyl)-7-methoxy-4H-1-benzopyran-4-one); 6'''-feruloyl-spinosin; isospinosin; spinosin; jujuboside A and jujuboside B. Later new phenylglycoside named Jujuphenoside from seeds of *Z.jujube* were also isolated<sup>7</sup>.

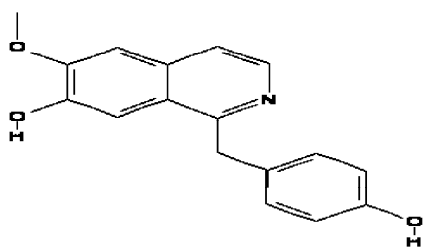


Fig 8: Juzirine

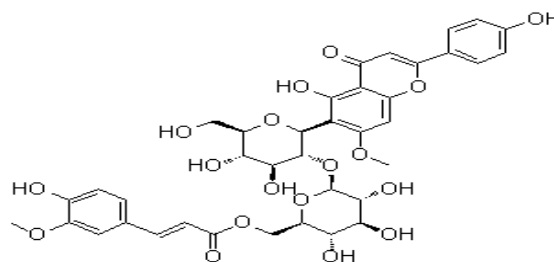


Fig 9: 6'''-Feruloylspinosin

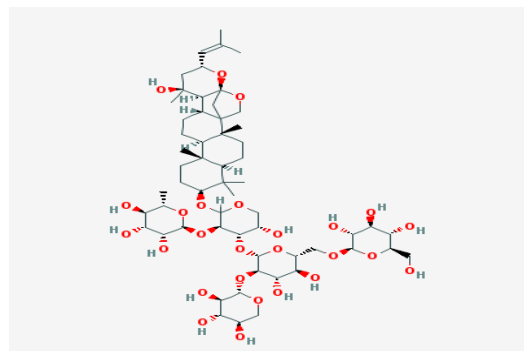


Fig 10: Jujuboside A

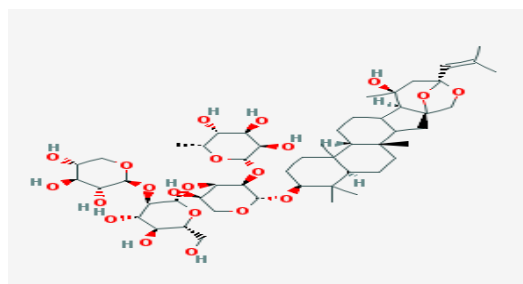


Fig 11: Jujuboside B

Plant polyphenols are secondary metabolites that can range from simple molecules, such as phenolic acids, to highly polymerized constituents such as tannins. All the phenolics, and particularly flavonoids, have been reported to have significant biological effects.

Pawlowska *et al.*, 2009 investigated flavonoids profile of *Z.Jujube*. The result revealed that methanolic extract have been recognized 12 compounds as quercetin, kaempferol, and phloretin derivatives by means of HPLC/ESI-MS analyses<sup>8</sup>.

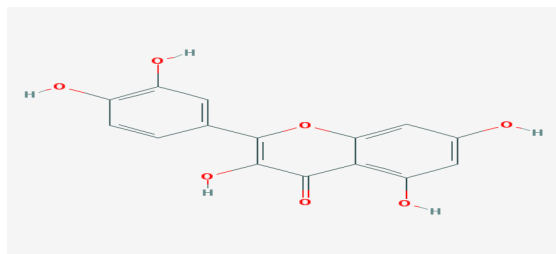


Fig 12: Quercetin

**Z.nummularia:**

Pandey *et al.* 1984, confirms the presence of cyclopeptide alkaloids from *Z.nummularia* which are peptide alkaloids nummularine-M and nummularine-N and their structures elucidated. Nummularine-M is a 14-membered cyclopeptide and belongs to the integerrinine type, whereas nummularine-N is a 13-membered cyclopeptide like nummularine-B<sup>9</sup>.

**Z.spina-christi**

Steroids,  $\beta$ -sitosterol,  $\beta$ -D-glucoside, condensed tannins, and four saponins glycosides, namely 3--L-

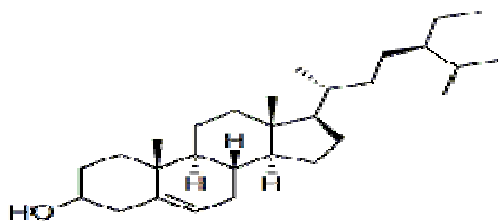
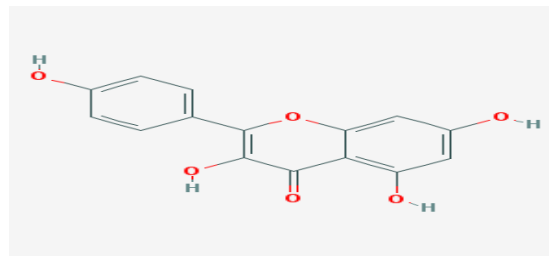
Fig 14:  $\beta$ -Sitosterol

Fig 13: Kaempferol

fucopyranosyl (1-2) -P-D-glucopyranosyl[L-airabinopyranosyl] jujubogenin, 3-0-[D-fucopyranosyl], Dglucopyranosyl-4- sulphate(1-3) L-arabinopyranosyl] jujubogenin, Dglucopyranosyl (1-2) L-rhamnopyranosyl (1-3) L-arabinopyranosyl] jujubogenin. Jujubogenin have been successfully isolated from the leaves. The free sugars like fructose, raffinose, sucrose, glucose, galactose, rhamnose were also isolated from different parts of the plants<sup>10</sup>.

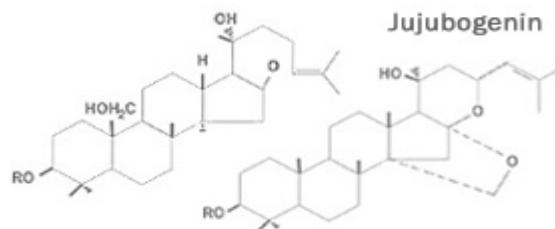


Fig 15: Jujubogenin

**PHYTOPHARMACOLOGY OF Z.JUJUBE****Antioxidant activity**

The term 'antioxidant' refers to the activity to protect against the damage caused by ROS (free radical) by the help of numerous vitamins, minerals, and other phytochemicals. By their ability to react with many damaged structures in the body, ROS are involved in various physiological mechanisms and conditions such as ageing, cancer, diabetes and atherosclerosis etc. Numerous studies have established that showed *Z.jujube* exhibited potent antioxidants<sup>11</sup>.

Kar *et al.*, 2013 reported antioxidant activity of methanolic extract of the leaves of the plant *Z. jujube* and they also determined the phenolic content of methanolic extract which was found to be 2.8%. The antioxidant activity showed very showed potential result in both tested methods that is 2,2-diphenyl-1-picrylhydrazyl (DPPH) and ferric ion reducing

capacity. The antioxidant activity is directly associated due to the presence of total polyphenol<sup>12</sup>.

**Antimicrobial**

Study was undertaken by imran *et al.*, 2014 to check the antimicrobial efficiency of crude leaves extract of *Z.jujube* and result indicates high potency against *Salmonella* and *staphylococcus aureus* infections, moderate activity against *P. aeruginosa*, *B. pumalis* and *E. aerogens* and low against *S. typhi*, *S. epidermidis*, *S. pneumoniae*, *S. aureus* and *K. pneumoniae*<sup>13</sup>.

The *Ziziphus* species are considered to be multipurpose plants and have been used as foods, folklore medicines, the environmental protection plants. As crude leaves extract showed potent antimicrobial efficacy, to scientifically prove this Sherif *et al.*, 2013 isolate and evaluated the antimicrobial activity of ethanol extract of *Z.jujube* seeds against six bacterial strains by determining

minimum inhibitory concentration (MIC) and analyzed their phytoconstituent content by using chromatographic techniques to identify the principal bioactive phytochemicals. Further, GC/MS analysis of ethanol extract of *Ziziphus jujuba* seed revealed the existence of 20 component, main components were 13-Heptadecyn-1-ol (12.95%), 7-Ethyl-4-decen-6- one (9.73%), Lineoleoyl chloride (8.54%), Linoleic acid (6.37%), 2,5-Octadecadiynoic acid, methyl ester (5.57%) and Palatinol A (4.81%). The results indicated that the ethanolic extract of *Ziziphus jujuba* seed contains a many bioactive components that could have advantage offer a platform of using *Ziziphus jujuba* seed as herbal alternative for the current synthetic antimicrobial agents having various side effects<sup>14</sup>.

### Sedative effect / Insomnia

*Z.jujube* (seed) are medicinally used in the insomnia. Jiang *et al.*2007, were investigated the hypnotic and sedative effect of three compounds flavonoids, saponins and polysaccharides. During their study extract was orally administrated to mice . The result revealed that flavonoids and saponins showed the significance response .Further comparative analysis showed that saponins had more effective sedative and hypnotic function than that of the flavonoids<sup>15</sup>.

### Antipyretic

The antipyretic effect was comparable with that of a standard paracetamol. Thus above finding justified that methanolic leaves extract of *Z.jujuba* developed to have therapeutic effects in antipyretic activity, or in the disease associated with increase in temperature<sup>15</sup>.

### Anti diarrheal

Hari *et al.*2012.,investigated anti-diarrhoeal efficacy of aqueous leaves extract by using castor oil and MgSO<sub>4</sub> (Magnesium sulphate) induced diarrhea model.The leaves extract showed significant inhibitory activity against castor oil and MgSO<sub>4</sub> induced diarrhea. The results obtained of the study showed that there was significant reduction in gastro intestinal motility by the charcoal meal test in rats. The final outcome of this studied substantiate the anti diarrhoeal effects of the aqueous extract<sup>16</sup>.

### Anti diabetic

In one of the study Balakrishnan *et al.*, 2013 investigated the effect of methanolic extract of dried bark of *Z.jujuba* extracts on blood glucose and lipid profile in streptozotocin induced diabetic rats . The

methanolic extract of *Z. jujube* was administered the doses caused a significant decrease in the levels of total cholesterol, triglycerides and LDL-cholesterol, glucose level. The results signify that methanolic extract of *Z.jujuba* in the dose dependent manner acquire hypoglycaemic and hypolipidemic activity<sup>17</sup>.Suttisri *et al.*,1995, isolated triterpenoid from leaves *Z. jujuba* which act as sweetness inhibitors and have been found to suppress sweet taste sensation in fly (*Pharma regina*), rat and in hamster. The anti-sweet substances isolated included jujubosaponins II, III, IV, V and VI from the leaves, jujuboside B from the leaves and seeds and ziziphosaponins I-III from dried fruit. Ziziphin and jujubosaponins II and III, the only three of the anti-sweet saponins from this plant with acyl groups, were up to 4 times more active in suppressing the sweet taste of sucrose than the other anti-sweet constituents and thereby reducing obesity in diabetic or overweight people<sup>18</sup>.

### Improve Immunity

Ganachari *et al.*,2004 studied the effect of hydroalcoholic extract of *Z.jujuba* leaves on neutrophil phagocytic function. The result showed that *Z. jujuba* leaves extract has stimulated chemotactic, phagocytic and intracellular killing potency of human neutrophils at the concentration range of 5-50µg/ml. The above finding concluded that the hydroalcoholic extract of *Z. jujuba* leaves stimulates cell-mediated immune system by increasing neutrophil phagocytic function<sup>18</sup>.

Rekha *et al.*,2014 was designed study to assess the anti-fertility effect of Petroleum ether leaves extract of *Z. jujuba*. This study was intended to assess the effect of petroleum ether leaves extract of *Z. jujuba* on sperm morphology, progressive motility and sperm concentration irreversibly in Wistar rats. Extracts were found to produce significant inhibition of sperm motility and cause reduction in viability of sperm cell. The result of this studied revealed that *Z.jujuba* rigorously affects male animal fertility parameters<sup>19</sup>.

Dhananjay *et al.*,2013 carried out studied to elicited the anti-inflammatory effect of ethanolic fruit extract of *Z. jujube* by using carrageenan induced paw edema model. The ethanolic extract of *Z. jujuba* was injected and the result was compared with standard drug Indomethacin<sup>20</sup>.

### Diuretic activity

Diuretic activity of fruit extract of *Z. jujuba* in rats was evaluated by Kabra *et al.*,2013. In this study, the diuretic activity of Petroleum ether, Chloroform, Alcohol extract of *Ziziphus jujuba* was studied and

the activity was compared with furosimide as standard. The observation of outcome showed alcoholic extract exhibited significant diuretic activity as evidenced by increased total urine volume and the urine concentration of  $\text{Na}^+$ ,  $\text{K}^+$  and  $\text{Cl}^-$ . The results of this support the *Z. jujuba* use of as diuretic agent <sup>21</sup>.

### Wound Healing

Sampath *et al*, 2012 studied wound healing potential of methanolic bark extract of *Z. jujube*. The result revealed that group received high dose of extract (10%w/w) showed significant wound contraction (98.09%) on 24<sup>th</sup> day. Protein content was also increased in the treated group, which directly focus increased in collagen synthesis <sup>22</sup>.

### Anti Inflammatory

Naika *et al*, 2013 carried out the study on the anti-allergic activity of ethanolic extract of *Z. jujube*. Current investigation also reported possible mode of action. The effect of extract of *Z. jujuba* at different doses was simulated on studied animal models of asthma and allergy: a) milk induced eosinophilia and leukocytosis; b) compound 48/80 induced mast cell degranulation; and, c) active and passive cutaneous anaphylaxis. In addition, extract of *Z. jujuba*'s effect on sensitized guinea pig ileum (ex vivo) and tracheal chain preparations (*in vitro*) were investigated. Treatment with extract of *Z. jujuba* at all doses significantly prevented the milk-induced eosinophilia and compound 48/80 induced degranulation of mesenteric mast cells; decreased passive cutaneous and active anaphylactic reactions <sup>23</sup>.

In addition, extract of *Z. jujuba* inhibited acetylcholine as well as histamine induced tracheal chain contraction, and also antigen induced contraction of sensitized guinea pig ileum (Shultz-Dale inhibition test). Furthermore, it exhibited also free radicals scavenging activity (*in vitro*). The observed anti-allergic and anti-anaphylactic activity of extract of *Z. jujuba* may be largely through the stabilization of mast cells by the membrane presence of phytoconstituents such as steroidal saponins and flavonoids <sup>24</sup>.

### PHYTOPHARMACOLOGY OF *Z. NUMMULARIA*

Gupta *et al*, 2011, reported that nutritional, phytochemical content and antioxidant activity of ripe fruits of *Z. nummularia*. In their study fruits were quantitatively analyzed for the colorimetrically. Nutritional properties including moisture, fats, carbohydrates, proteins, ash content and mineral

content in terms of total phenolic, flavonoid and flavonol content in the fruits were also determined <sup>25</sup>.

### Hepatoprotective

*Z. nummularia* is another species of *Ziziphus* having various medicinal values from traditional system of ailments. Prashanthi *et al*, 2014 was evaluate the hepatoprotective activity of methanol extract derived from the *Z. nummularia* fruits. There was significant reduction in ALAT, ASAT and ALP levels in  $\text{CCl}_4$  induced hepatotoxicity in rats by oral administration of the extract. The preliminary phytochemical screening study was also carried out which revealed that the extract contains alkaloids, phenolic compounds, flavonoides and tannins. The presence of poly phenols and flavonoids support its antioxidant potential <sup>26</sup>.

### Antibacterial and Antifungal

Potent antibacterial and antifungal activity of *Zizyphus nummularia* against bacterial and fungal strains (*Staphylococcus aureus*, *Streptococcus pyogenes*, *Bacillus subtilis*, *Pseudomonas aeruginosa*, *Aspergillus niger*, *Aspergillus flavus*, *Candida albicans* and *Trichophyton rubrum*) was investigated by Gautam *et al*. The antimicrobial activity of aqueous and ethanol extracts was determined and results indicates ethanol extract as more potent than aqueous extract. The most vulnerable bacteria were *Staphylococcus aureus* and fungi *Trichophyton rubrum* <sup>27</sup>.

### Anti-diabetic

Anti-diabetic activity of ethanolic and aqueous extract of *Z. nummularia* was studied by Rajasekaran *et al*. Animals were induced for diabetes with alloxan and treated orally with ethanolic and aqueous extract of *Z. nummularia* results confirms its anti-hyperglycemic and hypolipidemic activity as compared to diabetic control. The extract shows advantageous effects on blood glucose.

It also reduces the elevated biochemical parameters such as triglycerides (TGL), low density lipoprotein (LDL), very low density lipoprotein (VLDL), total cholesterol (TC), increased the reduced level of high density lipoprotein (HDL) and maintain body weight. The histological study supports the results. Thus both extracts could serve as good oral hypoglycemic agents and seems to be promising for the development of phyto-medicines for diabetes mellitus <sup>27</sup>.

### Other activities



Traditionally, the genus *Z. nummularia* is used in treatment of mental retardation, preventing frequent attacks of influenza, colds, treating dysentery, diarrhoea and colic. It is also used in ulcers, fevers, wound healing, pharyngitis, bronchitis, burns, anaemia, irritability, hysteria and as a nervine tonic<sup>28</sup>.

#### PHYTOPHARMACOLOGY OF *Z. SPINA-CHRISTI*

The leaves contain various alkaloids and diverse saponins. Traditionally, the roots are used to treat headaches, while the spines or ashes of this species are applied to snake bites. Leaves have been used as wound healer. They also have antihelminthic and antidiarrhoeal efficacy. Leaves used to reduce eye inflammation<sup>29</sup>.

#### Anti Cancer

Different leaves extracts of *Z. spina-christi* were investigated cytotoxic effect on cancer cell lines. Various solvent like hexane, chloroform, chloroform-methanol (9:1), methanol-water (7:1) methanol, butanol and water were used for extraction, after preliminary phytochemical analyses were done. The cytotoxic activity of the extracts against HeLa and MDA-MB-468 tumor cells was evaluated by MTT assay. The result revealed that the extracts (concentration dependently) reduced viability of HeLa and MDA-MB-468 cells. The outcome of the above finding showed that chloroform-methanol extract of *Z. spina-christi* was more potent than the other extracts in both the cell lines<sup>29</sup>.

#### Anti fungal

Anti fungal activity of *Z.spina-christi* was evaluated against *Candida* species, especially *Candida albicans*, which are major fungal pathogens of humans that are capable of causing superficial mucosal infections and systemic infections in humans<sup>30</sup>.

#### Anti-diabetic

Study was under taken to evaluate the anti-diabetic activity of *Z.spina-christi* leaf extract, plain and formulated in STZ-diabetic rats. Percentage yield of extracts, marker yield (christinin-A) and antihyperglycemic potencies, depending on seasonal variation were investigated. The result revealed that *Z. spina-christi* leaf extract, plain and formulated, improved glucose utilization in diabetic rats by increasing insulin secretion which may be due to both saponin and polyphenols content and controlling hyperglycemia through attenuation of meal-derived

glucose absorption that might be attributed to the total polyphenols<sup>31</sup>.

#### Hepatoprotective

Carbon tetrachloride (CCl<sub>4</sub>)-induced hepatic fibrosis of the water extract of *Z. spina-christi* (ZSC) studied was carried out. Water extract were administrated for 8 weeks. The result (histo-pathological, biochemical and histology texture analyses) of above finding shows that ZSC significantly hinder the progression of hepatic fibrosis. ZSC resulted in a considerable amelioration of liver injury judged by the reduced activities of serum ALT and AST<sup>32</sup>.

#### Anti diarrheal

Methanolic stem bark extract of *Z.spina-christi* were evaluated antidiarrhoeal efficacy in laboratory rodents. The results showed that the extract possess a dose dependent protection of rats against castor oil induced diarrhoea, decreased the intraluminal fluid accumulation and gastrointestinal transit. It is suggested that the extract may contain biologically active components that may be useful against diarrhoea, thereby explanatory its use in ethnomedical practice as an antidiarrhoeal agent<sup>33-34</sup>.

#### CONCLUSION:

The genus *Ziziphus* can produce almost all type of bioactive compounds, which has a leading potential for the development of new good worth drugs in future as found in the literature survey. This genus exhibited many remarkable biological activities, thus for the identification, classification and documentation of plants a comprehensive and systematic medicinal study is required, which may provide a significant way for the encouragement of the traditional awareness of the herbal medicinal plants. On the basis of the reported pharmacological activity on the species (*Z. jujube*, *Z. nummularia* & *Z. spina-christi*) of genus *Ziziphus* open the gateway of the virgin areas of research to explore, isolate and identify the lead biomarkers compounds which could be useful for mankind against the various life threatening disease.

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