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Research Article

# Evaluation of Potential Toxicity of Bioactives of *Anagallis arvensis*- A Toxic Plant

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**ABSTRACT**

Toxic plants are found to have potential therapeutic activities. They have been used in the treatment of a number of diseases. Recently there is an increasing demand and interest in bioactive natural products from plants for the purpose of their use in herbal medicine. So critical evaluation of their toxicity has become necessary. This article provides the detailed toxicity information of the phytochemical constituents from the toxic plant A*nagallis arvensis* (Family Primulaceae). The plant is toxic to ruminants but it has great potential to treat diseases like Gout, Leprosy, Epilepsy, Urinary infection etc. The phytochemical constituents isolated from the toxic plant have Antibacterial, Antifungal, Antiviral, Antitumour, Antidiabetic, Antidepressant, Anti-inflammatory and Hepatoprotective activities. Some bioactives are having therapeutic activity, no reported toxicity and were predicted to be less toxic. Many actives from this plant have not been explored for any activity and their toxicity has not been determined. These actives were found to be less toxic through the toxicity prediction tool. This study would be important for exploiting the potential of such actives which may further prove to be promising natural products for medicinal and cosmetic use.

**Keywords:** *Anagallis*, Primulaceae, Toxicity, Prediction, Bioactive, Traditional medicine

## INTRODUCTION

Poisonous plants are distributed all over the world. Plants produce poisonous compounds as defensive mechanism. These plants can cause serious illness, injury, or death to humans or animals following accidental ingestion, skin contact, eye exposures or inhalation. Poisonous plants are used for different purposes such as hunting, fishing, wars and treating diseases. *Anamirta cocculus* is used for piscidal activity[1]. Poisonous plants are source of various drugs viz. Digoxin and Digitoxin from *Digitalis* spp. used as cardiotonic, Vincristrine and Vinblastine from *Catharanthus roseus* act as anticancer agent, Atropine from *Atropa belladonna* act as anticholinergic while morphine and codeine from *Papaver somniferum* act as analgesic[2]. Poisonous plants have also been proved as a source of bioactives showing therapeutic activity and lower toxicity. Bioactive compounds of known scaffold can be used to synthesize molecules showing higher therapeutic activity and lower toxicity e.g., metformin, nabilone, oxycodon (narcotic analgesics), taxotere[3]. There are still many poisonous plants in nature which are unexplored for their bioactivity. We have focused our study to one of such poisonous plant *Anagallis arvensis.* Toxic effect of *Anagallis arvensis* on humans has not yet been reported. Detail toxicity studies and clinical studies are not being carried out. Objectives of this article are: 1) Detail literature search for biological activity and toxicity of the active constituents of the plant, 2) Toxicity prediction of the actives using DEREK.

## MATERIALS AND METHODS

The literature search for biological activity and toxicity of the plant was carried out on free and subscribed databases viz. Toxnet, PubMed and SciFinder.

***In silico Toxicity Prediction***

Toxicity of the actives for which there was no existing toxicity data was predicted using DEREK Nexus version 4.1.0, Nexus: 2.0.0. DEREK is a knowledge based expert system which predicts the potential toxicity of molecules. The qualitative predictions made by DEREK are based on rules and reasonings which describe the relation between chemical structure and toxicity.

## RESULTS AND DISCUSSION

On searching the existing toxicity data for the whole plant and its active constituents, it was found that the plant is toxic to cattle and sheep. Plant is reported to produce gastrointestinal symptoms in dogs and horses. It is also toxic to poultry animals, rabbits and birds. Clinical signs include difficulty in breathing, stiffness in gait, leg weakness, and recumbancy. Post mortem lesions are haemorrhage in kidney, heart and intestine, congestion of lung and liver. In another case reported by Riet-Correa[4] four cases of poisoning were diagnosed in barely and stubble field. Cattle of different ages were affected. Morbidity was 7-30% and fatality was 50-86%. LD50 of the extract was determined by dosing rats intraperitoneally at the dose of 5, 10, 20, 40 mg/kg body weight. LD50 was

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Table 1: The reported toxicity and biological activities of the plant bioactives.

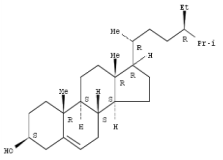
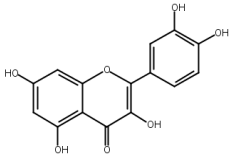
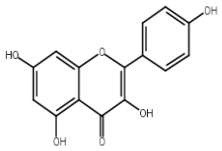
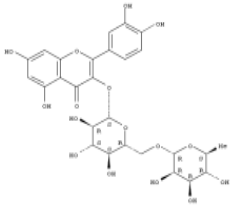
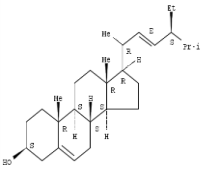
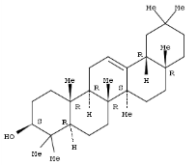
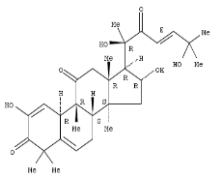
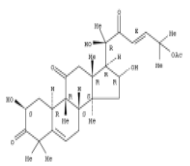
| Sr. No. | Active name and CAS No. | Phytochemical groups | Structure | Toxic endpoints | Biological activity |
|---|---|---|---|---|---|
| 1 | Beta Sitosterol (83-46-5) | Saponin |  | Acute/ subacute toxicity[7], Developmental toxicity[8] | Anticancer[9], Angiogenic activity [10], Antihyperglycemic activity[11] |
| 2 | Quercetin (117-39-5) | Saponin |  | Acute toxicity [12], Developmental toxicity[13], Genotoxicity[14], Neurotoxicity[15] | Chelating and free radical scavenging activities[16], Antioxidant activity[17], Anti-inflammatory activity[18], Antidiabetic activity[19], Anticancer activity[20] |
| 3 | Kaempferol (520-18-3) | Saponin |  | Acute toxicity[21], Developmental toxicity[22], Genotoxicity [23] | Hepatoprotective effects[24], Antibacterial activity[25], Anti-asthmatic effect[26], Anxiolytic activity [27], Treatment of atherogenesis[28] |
| 4 | Rutin (153-18-4) | Triterpene |  | Acute toxicity[29], Developmental toxicity[30], Genotoxicity [31] | CNS depressant[32] Antinociceptive effects[33], Antihyperglycemic Effect[34], Hepatoprotective activity [35], Anthelmintic, antibacterial, antifungal, cytotoxic, larvicidal[36] |

Table 2: summarizes biological activity, reported toxicity and toxicity prediction for those actives which have less or no reported toxicity.

| Sr. no | Actives Name and CAS No. | Phytochemical groups | Structure | Toxic endpoints | Biological activity | Prediction/ likelihood |
|---|---|---|---|---|---|---|
| 1 | β-Stigmasterol (83-48-7) | Saponin |  | Acute Toxicity[37] | Thyroid inhibitory, antiperoxidative and hypoglycemic effects [37], spasmolytic and anti-inflammatory [38], Viper and cobra venom neutralization[39], antitumor[40] | No alert |
| 2 | Beta Amyrin (559-70-6) | Triterpenoid |  | Acute Toxicity[41] | Anxiolytic and antidepressant effects[42] | Nephrotoxicity, Skin sensitisation |
| 3 | Cucurbitacin I (2222-07-3) | Triterpenoid |  | Acute toxicity[43] | Antitumor[44] | Carcinogenicity, Hepatotoxicity, Nephrotoxicity, Skin sensitisation |
| 4 | Cucurbitacin B (6199-67-3) | Triterpenoid |  | Acute toxicity[45] | Anti-inflammatory[46] anti-cancer[47] | Carcinogenicity, Nephrotoxicity, Skin sensitisation |

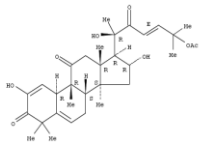
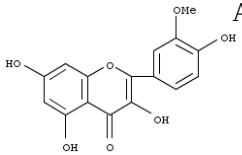
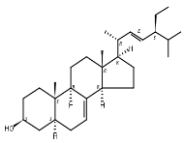
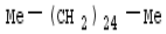
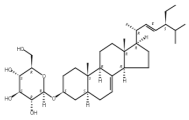
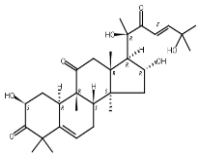
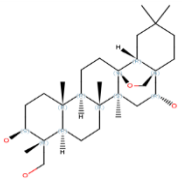
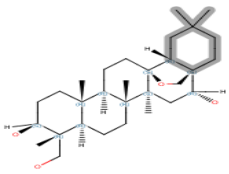
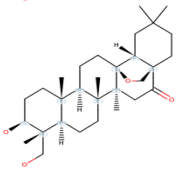
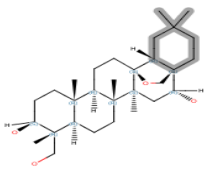
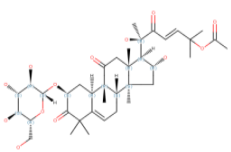
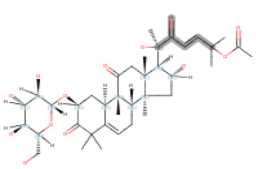
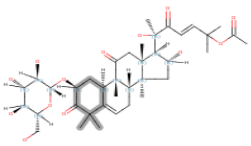
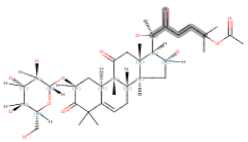
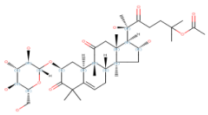
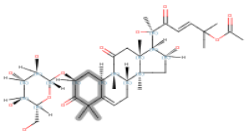
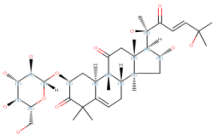
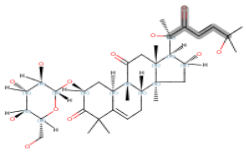
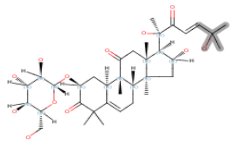
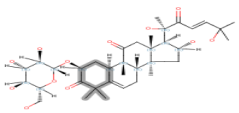
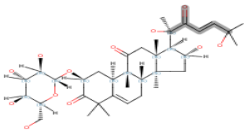
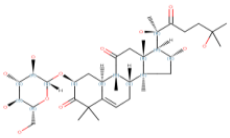
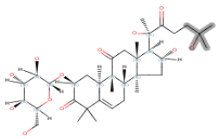
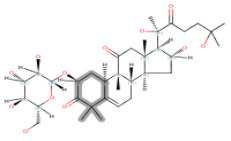
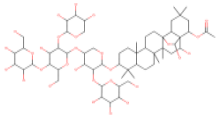
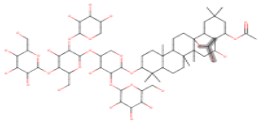
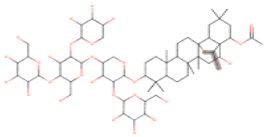
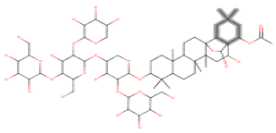
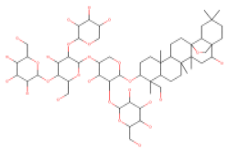
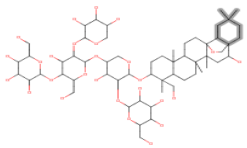
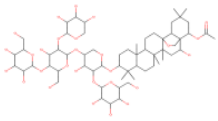
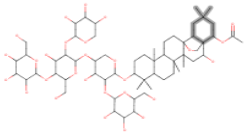
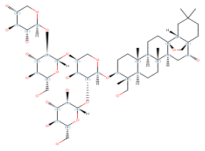
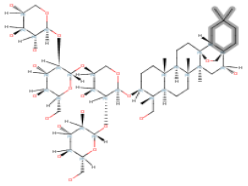
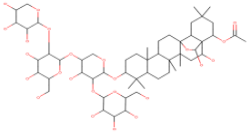
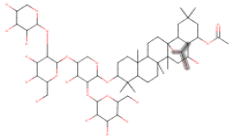
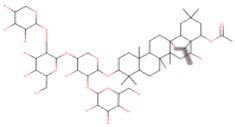
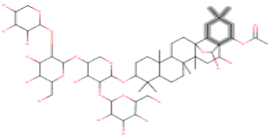
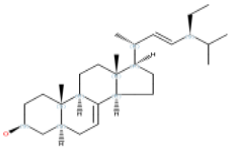
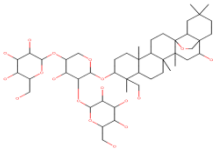
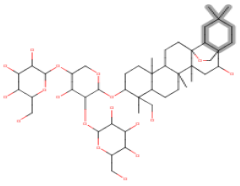
| | | | | | | |
|---|---|---|---|---|---|---|
| 5 | Alpha Elaterin (18444-66-1) | Triterpenoid |  | Acute toxicity[45] | Anti-inflammatory[48] | Carcinogenicity, Skin sensitisation |
| 6 | Isorhamnetin (480-19-3) | Flavonoid glycoside |  | Acute toxicity[49] | Anti-tumor[50] | Chromosome damage in vitro, Mutagenicity in vitro, Skin sensitisation |
| 7 | α-spinasterol (481-18-5) | Higher alkanes |  | Acute toxicity[51] | Antinociceptive [52] | No alert |
| 8 | n-hexacosane (630-01-3) | Lipid |  | Acute toxicity[53] | Anti-inflammatory[53] | No alert |
| 9 | α-Spinasterol glucoside (1745-36-4) | Steroids |  | Not available | Anti-inflammatory[54] | No alert |
| 10 | Cucurbitacin D (3877-86-9) | Phytosterols |  | Not available | Anti-tumor[55], treatment of β-hemoglobinopathies, including sickle cell anemia and β-thalassemia[56], immunomodulating activity[57] | Carcinogenicity, Hepatotoxicity, Nephrotoxicity, Skin sensitisation |

Table 3: provides a list of the actives with no reported toxicity and biological activity with their toxicity predictions. Substructures which might have the toxicity potential are highlighted.

| Sr. no | Actives Name and CAS No. | Structure of active | Matching alert | Matching alert detail | Prediction/ likelihood |
|---|---|---|---|---|---|
| 1 | Lacceric acid (3625-52-3) |  | -- | No alert | -- |
| 2 | Anagalligenin B (33722-92-8) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 3 | Anagalligenone B (33809-48-2) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 4 | Arvenin I (65247-27-0) |  |  | alpha,beta-Unsaturated aldehyde, ketone or imine | Carcinogenicity |

| | | | | | |
|---|---|---|---|---|---|
| | | |  | 1,1-Dimethylcyclo-hexane | Nephrotoxicity |
| | | |  | alpha,beta-Unsaturated ketone or pre-cursor | Skin sensitisation |
| 5 | Arvenin II (65247-28-1) |  |  | 1,1-Dimethylcyclo-hexane | Nephrotoxicity |
| 6 | Arvenin III (65597-45-7) |  |  | alpha,beta-Unsaturated aldehyde, ke-tone or imine | Carcinogenicity |
| | | |  | Tertiary alcohol or ether | Hepatotoxicity, Nephrotoxicity |
| | | |  | 1,1-Dimethylcyclo-hexane | Nephrotoxicity |
| | | |  | alpha,beta-Unsaturated ketone or pre-cursor | Skin sensitisation |
| 7 | Arvenin IV (69312-48-7) |  |  | Tertiary alcohol or ether | Hepatotoxicity, Nephrotoxicity |
| | | |  | 1,1-Dimethylcyclo-hexane | Nephrotoxicity |
| 8 | Anagalloside A (114318-81-9) |  |  | Alkyl aldehyde or precursor | Chromosome dam-age in vitro, Muta-genicity in vitro, Non-specific geno-toxicity in vitro |

| | | | | | |
|---|---|---|---|---|---|
| | | |  | Aldehyde pre-cursor | Skin sensitisation |
| | | |  | 1,1-Dimethylcyclo-hexane | Nephrotoxicity |
| 9 | Anagalloside B (114318-82-0) |  |  | 1,1-Dimethylcyclo-hexane | Nephrotoxicity |
| 10 | Anagalloside C (114318-83-1) |  |  | 1,1-Dimethylcy-clohexane | Nephrotoxicity |
| 11 | Deglucoanagallo-side B (114318-84-2) |  |  | 1,1-Dimethylcy-clohexane | Nephrotoxicity |
| 12 | Deglucoanagallo-side A (114333-17-4) |  |  | Alkyl alde-hyde or pre-cursor | Chromosome dam-age in vitro, Muta-genicity in vitro, Non-specific geno-toxicity in vitro |
| | | |  | Aldehyde pre-cursor | Skin sensitisation |
| | | |  | 1,1-Dimethylcy-clohexane | Nephrotoxicity |
| 13 | Dihydrospinaster-ol (117598-82-0) |  | -- | No alert retrieved | -- |
| 14 | Anagallisin E (136825-40-6) |  |  | 1,1-Dimethylcy-clohexane | Nephrotoxicity |

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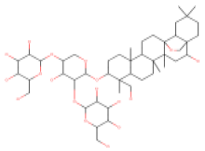
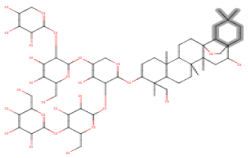
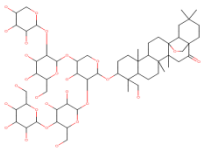
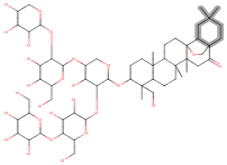
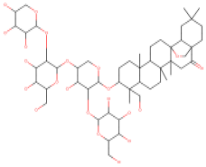
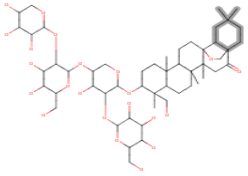
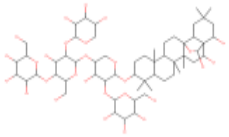
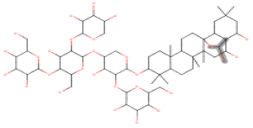
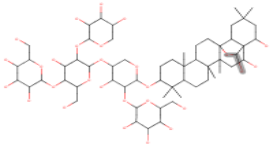
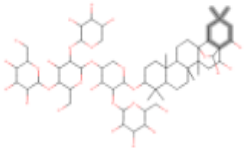
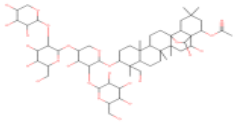
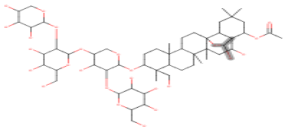
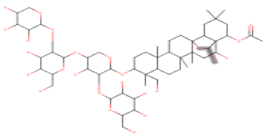
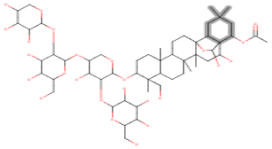
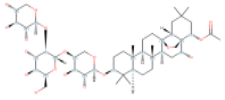
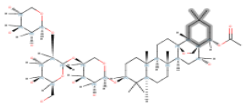
| 15 | Anagallisin A (136842-05-2) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 16 | Anagallisin B (136842-06-3) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 17 | Anagallisin D (136842-07-4) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 18 | Anagallosaponin I (162762-99-4) |  |  | Alkyl aldehyde or precursor | Chromosome damage in vitro, Mutagenicity in vitro, Non-specific genotoxicity in vitro |
| | | |  | Aldehyde precursor | Skin sensitisation |
| | | |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 19 | Anagallosaponin II (162763-00-0) |  |  | Alkyl aldehyde or precursor | Chromosome damage in vitro, Mutagenicity in vitro, Non-specific genotoxicity in vitro |
| | | |  | Aldehyde precursor | Skin sensitisation |
| | | |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 20 | Anagallosaponin III (162763-01-1) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |

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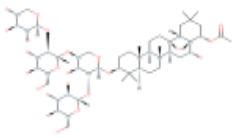
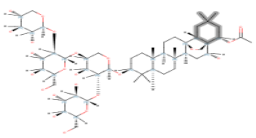
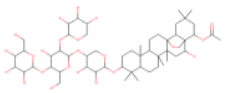
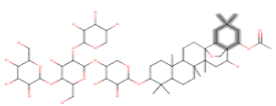
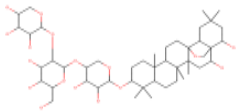
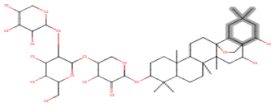
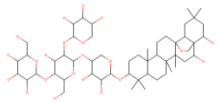
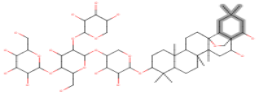
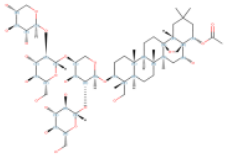
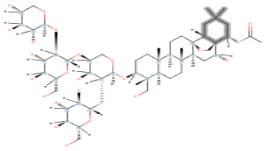
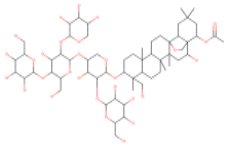
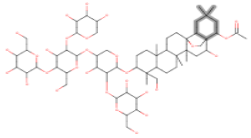
| 21 | Anagallosaponin IV (162763-02-2) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 22 | Anagallosaponin V (162763-03-3) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 23 | Anagallosaponin VI (160669-21-6) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 24 | Anagallosaponin VII (160632-42-8) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 26 | Anagallosaponin VIII (160632-43-9) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 27 | Anagallosaponin IX (160632-44-0) |  |  | 1,1-Dimethylcyclohexane | Nephrotoxicity |
| 28 | Anagalline | _ | _ | - | - |
| 29 | Sanagalligenone | _ | _ | - | - |

calculated according to Weill method. LD50 of alcoholic extract was found to be 10.718 mg/kg b.wt[5].

Studies conducted on rats have shown that whole plant possesses antispermicidal and semen coagulation activity[6].

*Toxicity prediction for the active constituents*

Out of total forty three actives studied, only twenty nine actives possess less literature data with respect to their biological activity or toxicity. These actives were run in the DEREK software for toxicity prediction. Alerts were fired for nephrotoxicity, carcinogenicity, hepatotoxicity, skin sensitization, chromosome damage and mutagenicity in vitro. This plant contains many actives which are not yet reported for any biological activity and have no reports of toxicity. These actives were run in DEREK software for toxicity prediction.

*Anagallis arvensis* is known to be a toxic plant but it has many beneficial effects. This plant has been traditionally used for therapeutic purpose. Many actives from this plant are not explored yet for any biological activity and their toxicity has not been determined. Toxicity prediction of these actives have not revealed any major toxicities. There are many drugs and their synthetic counterpart in use, which are based on the framework of compounds derived from plants. So it is important to have an awareness about the toxic medicinal plants to get their maximum therapeutic benefit. This study is an effort in this direction and is open for further research.

**ACKNOWLEDGMENTS**

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