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Original Research

In-silico analysis of Patentiflorin A – a potent drug from *Justicia gendarussa*

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ABSTRACT:

Justicia gendarussa is a highly valuable ethno medicinal plant. Due to the identification of the novel chemical constituent Patentiflorin - A, it has been more popularized for the treatment of HIV-AIDS. This potent drug has been analyzed using *in-silico* tools and servers for understanding its therapeutic nature. In this analysis, we found that it is used to treat a variety of ailments including cancer, rheumatism, allergy, Alzheimer's disease, Parkinson's disease, Gaucher disease, Charcot-Marie-tooth disease, common cold, liver disease and cardiac arrest etc., This research is fruitful as most of its hidden uses are understood.

Keywords:

Justicia gendarussa, Patentiflorin-A, Anticancer, Antibiotic, Cardioprotective and PASS.

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INTRODUCTION

Plants have been the major source of drugs in Indian system of medicine and other ancient systems in the world. The Indian tradition has an ancient heritage of traditional medicine. Indian traditional medicines are based on various systems including Ayurveda, Siddha, Unani and Homeopathy. With the rising overall enthusiasm for adopting and contemplating conventional methods and utilizing their potential depending on various health care systems, the assessment of the rich legacy of customary medicine is vital. Most of the commonly available plants in India are highly valuable for its medicinal potential. *Justicia* sp is one among such useful plants.

Justicia gendarussa, usually referred as willow-leaved Justicia, is a small erect and branched shrub. It has been portrayed as uncommon and endemic to India, and is broadly utilized in different forms for a significant number of its therapeutic and insecticidal properties (Agastian *et al*., 2006). It is a fast growing, evergreen shrub of the forests viewed as a commonly available plant of China, Sri Lanka, India and Malaysia. (Dennis and Hoshino, 2010). This plant is usually collected from the wild for therapeutic use as a medication and insect repellent and are also grown as an ornamental plant (Prosea, 2019).

It is said to be useful against asthma, rheumatism and colics of children (William *et al*., 1893). It has the potential to be the basis for a birth control pill for men (GlobalPost, 2011; PBS, 2011; Coconuts Jakarta, 2014) The enzymes vital for the growth of HIV is inhibited by the compounds present in this plant (Hong-Jie *et al*., 2017; University of Illinois at Chicago, 2017). During the last few decades, numerous secondary metabolites of plants were identified for the formulation of potent anti-HIV drugs. Although there is yet no cure for HIV, antiretroviral therapy significantly slows down the progression of the virus. The first drug to have been approved in the fight against AIDS is azidothymidine (AZT).

Since 1987, however - the year in which AZT was approved by the US. Food and Drug Administration (FDA) - the virus has adapted to the drug. Today, HIV patients are given a combination of various drugs, of which AZT is often still the main component. Compounds possessing biological activity were isolated using the most common bioassay guided isolation techniques which were used for the extraction of the anti-HIV arylnaphthalene lignin glycoside or patentiflorin-A from the root and stem extracts of *J. gendarussa* (Sandoiu, 2017)

Patentiflorin-A, an anti-HIV arylnaphthalene lignin (ANL) glycoside was available at the plant stem and root. The quinovopyranosyloxy group present in the structure of these compounds was found to retain the anti-HIV activity. The reverse transcription process in HIV-1 was inhibited by patentiflorin-A on a study carried against R/U5 and U5/gag transcripts of HIV-1 gene expression. The nucleotide (AZT) and non – nucleotide analogue (nevaripine) of the drug resistant HIV-1 isolates were also inhibited by patentiflorin-A (Hong-Jie *et al*., 2017).

But in the *in silico* studies, it is revealed that it is a potent drug for the treatment of cancer as well as cardiovascular disorders. It is proved to be an

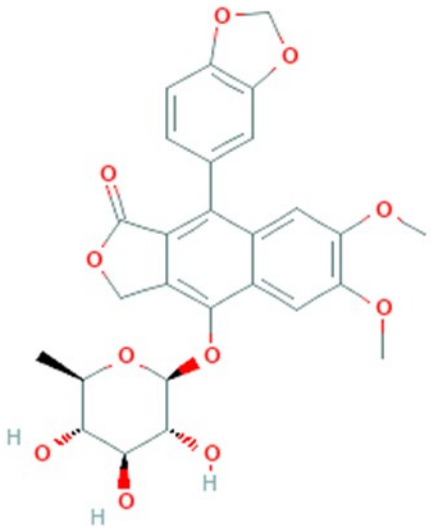

Figure 1. Chemical structure of Patentiflorin-A

Table 1. Chemical and physical properties of Patentiflorin-A computed by PubChem 2.1 (NCBI, 2006)

S. No	Property name	Property value
1	Molecular weight	526.5 g/mol
2	XLogP3-AA	2.3
3	Hydrogen bond donor count	3
4	Hydrogen bond acceptor count	11
5	Rotatable bond count	5
6	Exact Mass	526.147512 g/mol
7	Monoisotopic mass	526.147512 g/mol
8	Topological polar surface area	142²
9	Heavy atom count	38
10	Complexity	857
11	Defined atom stereocenter count	5
12	Covalently-bonded unit count	1
13	Compound Is canonicalized	Yes

antifungal, anti bacterial, antiviral and anti-rheumatic agent. But, if the drug is administered without making a concoction or cocktail with the other potent drugs then it may not be a promising drug molecule to treat HIV as no traces of functionality was found in this regard.

***In-silico* analysis**

In the therapeutic chemistry for the biocidal application, the oxygen and heteroation in the heteroatom compound ring is the main key factor. Scientists throughout the world are much interested in synthesizing new drugs for investigating these therapeutic properties. Due to reduced efficiency, harmful pharmacological toxicities and non-appropriate pharmacokinetic properties, there are major flops in the drug Research and Development (R and D) (Agastian *et al*., 2006). In the Research and Development of new drugs, complete failure of the project was due to the side effects and toxicity that are identified very late and the unknown existing prospective activities. Sometimes, new action of old compounds is also found during clinical trials or practical use of medicine, and that becomes a reason for new indication of drug.

Keeping these aspects in the failure of drug research and development project and importance of this drug in the medicinal chemistry, we have investigated the possibilities of utilizing computer aided prediction to estimate the general biological potential of Patentiflorin-A. Decades back, Computer Aided Drug Design (CADD, 2013) was started to be used in new drug Research and Development (Franke and Herrmann, 1994). Such a novel computerized system - PASS (Prediction of Activity Spectra for Substance) estimates simultaneously the probability of more than 100 pharmacological activity, effects and mechanisms (Filimonov *et al*., 1995 and 1996; Filimonov and Poroikov 1996). Therefore, the present study was designed towards the Prediction *of Activity Spectra* for the champion compound "Patentiflorin-A" which is now popular for its anti-HIV potentials.

MATERIALS AND METHODS

Chemical compound

To suppress and prevent AIDS virus, patentiflorin-A, a novel anti-HIV agent could be added to the anti-viral drug cocktail regimens which are used nowadays. Figure 1 Shows the chemical structure of Patentiflorin-A.

Brief description of PASS

With an average accuracy of about 85% in the Leave-One-Out Cross-validation (LOOCV) based on the structure of the chemical compounds, 780 or higher pharmacological impacts, mutagenicity, carcinogenicity, embryotoxicity teratogenicity and the mode of action were predicted by PASS (University of Illinois at Chicago, 2017; Hong-Jie *et al*., 2017; Sandoiu, 2017). Utilization of PASS program for above half million compounds were portrayed. Incorporating common pharmacological impacts, explicit mode of activity, known toxic levels, etc. About 565 different types of activities were added. Utilization of this web-based computer applications for answering the different types

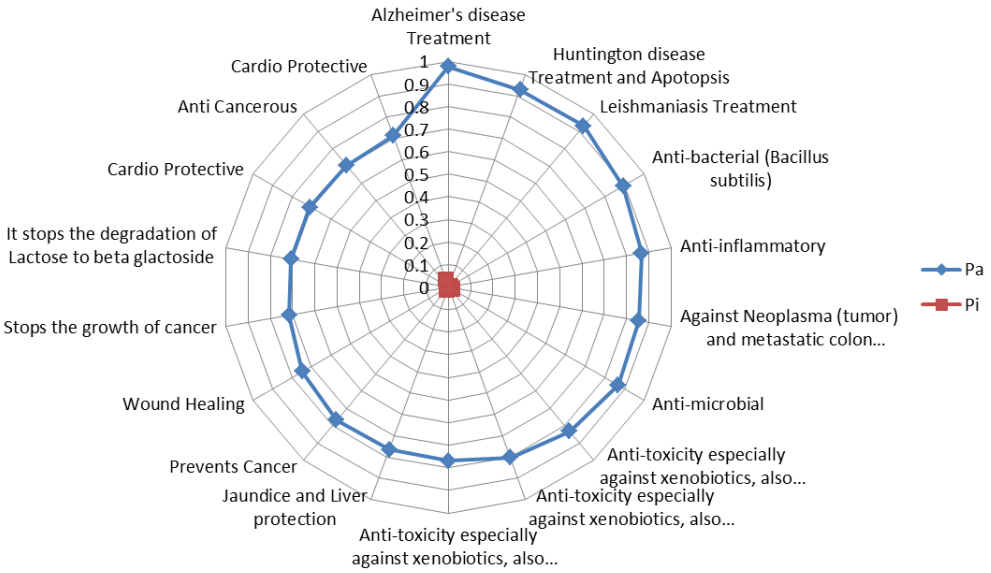

Figure 2. Antagonic effects of the drug Patentiflorin-A against various ailments at its most possible activity profile predicted by PASS server with Pa> 70%

of activites especially angiogenesis inhibitor or anti-viral (HIV) and a lot of properties with antineoplastic activity are associated for and the results of prediction by PASS are automatically displayed in the server. PASS provides data with respect to the following

1. From the in-house and commercial databases, the most plausible new leads with required spectra of the active compounds.

2. From corporate and private databases, new impacts and mode of action of the known old compounds.

3. Relevant assays for a specific compound (Salama and El-Essa, 2001; Nizamuddin *et al*., 2001; Suja *et al*., 2005; Margita *et al*., 1998).

Basic elements of PASS

(i) Training set

About 46,000 biologically active compounds were in PASS tracing package. This currently comprises around 16,000 drugs which were already under clinical trials and 30,000 drug candidates.

(ii) A description of the chemical structure

The original descriptors called Multilevel Neighborhood of Atoms (MNA) was developed for the description of the chemical structure in PASS (Garporova *et al*., 1997). MNA is generated by the compounds based on the table of connections and of the types of atoms.

(iii) A description of biological activity

The interactions between the chemical compounds and the biological entity is usually referred as the biological activity. Human body represents biological entity in clinical research. Every biologically active compound displays broad range of different effects. A variety of biological active compounds are used for treating diseases while many others end up in toxic side effects. Biological activity spectrum of a drug, given the disparity in critical condition of its experimental determination, defines each of its activities.

(iv) Spectrum of bioactivity

The continuum of biological activity is a term that is vital to PASS and that provides the reason for predicting other forms of biological activity for different compounds. Biological behaviour within this definition is

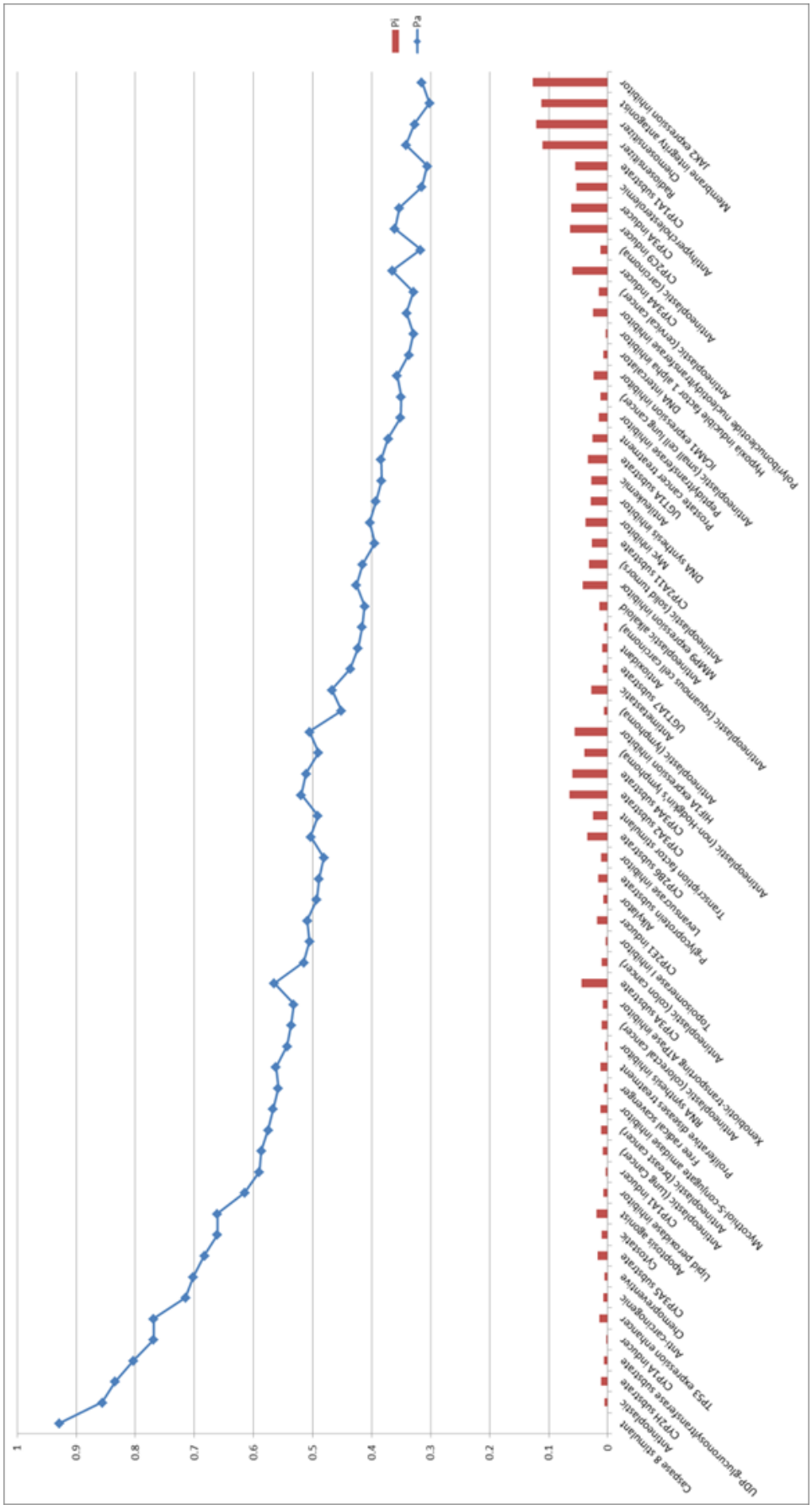

Figure 3. Anti cncerous effects predicted in the compound Patentiflorin A

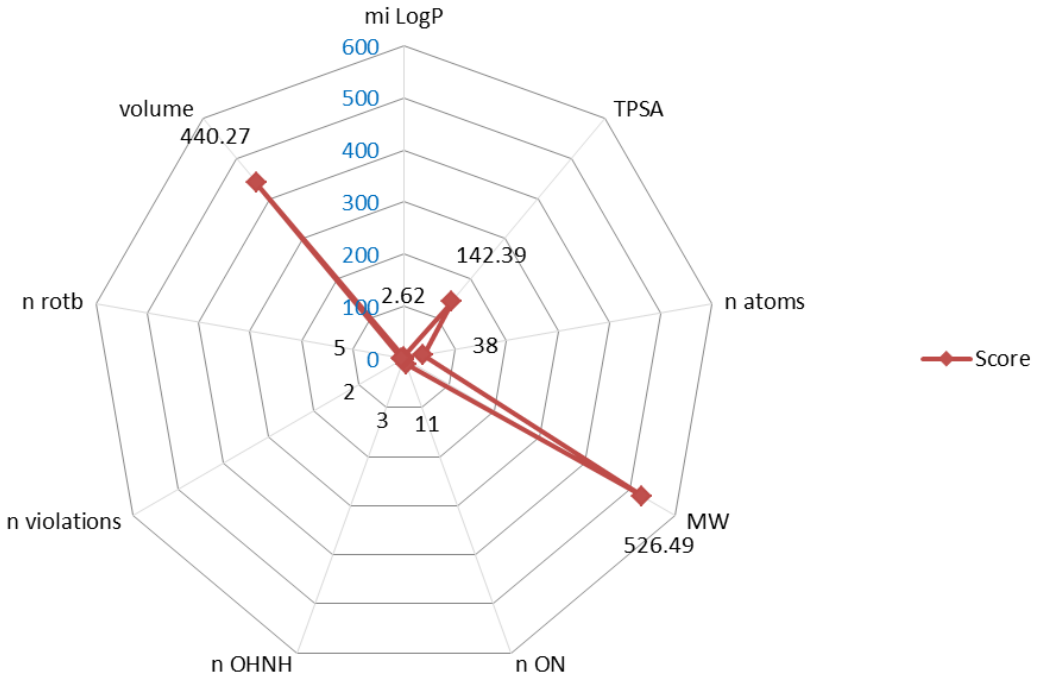

Figure 4. Properties of the molecule as predicted by Molinspiration

known to be an intrinsic property of the compound only depending on its structure (Nohara *et al*., 1974; Nohara *et al*., 1973; Reynolds and Allan, 1969). Therefore, one may use PASS to predict the spectrum of biological activity for existing compounds and unknown compounds. By making use of a qualitative representation of biological behaviour, data obtained from several different sources can be combined with the same. To reveal the mode of action and the effects of any compound that is planned to be synthesized, the prediction of their biological activity spectrum must be done (Figure 4).

Prediction of bioactivity score

To be a prospective compound/candidate for drug use, drug score values can be used. The bioactive score of the phytochemicals in the human receptors such as ion channels, kinases, GPCRs, nuclear receptors, enzymes and proteases can be predicted using the web based tool, Molinspiration (Proudfoot, 2002). If the bioactive score is >0, then it is a active compound, whereas if it is between −5.0 and 0.0, then the complex is moderately active and if the score for bioactivity is less than −5.0, then it is inactive (Verma, 2012) (Figure 5).

RESULTS AND DISCUSSION

Assessment of biological activity spectra based on the compound structure was done using PASS with the same set of MNA descriptors. The compounds are viewed as equal for those with stereo chemical – structural differences; this is because the stereochemical peculiarities of the compounds were not represented by the MNA descriptors. The equivalent structures are excluded from the training set during the PASS prediction.

The list of activities with appropriate Pa and Pi, was arranged in the descending order of the difference (Pa-Pi) > 0, which was the result of the prediction. For each mode of action in any biological activity spectra, 'Pa' and 'Pi' are the estimates of probability for the active and inactive compounds with their values ranging from 0.0 to 1.0. The activities of those compounds with Pa > Pi will only be revealed in the bio-active spectra.

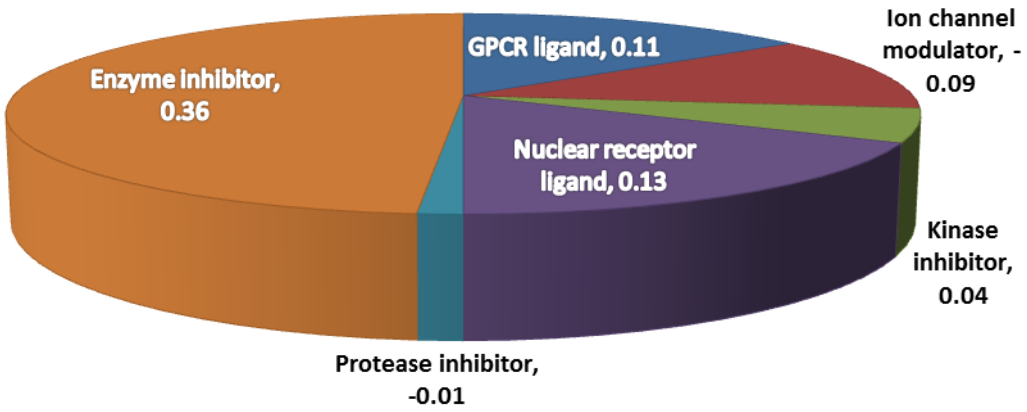

Figure 5. Molinspiration bioactivity score

- The analogue of the identified pharmaceutical compound is high, if Pa > 0.7 and is considered very likely to reveal their mode of action in the experiments.
- The compound is considered not similar to the identified pharmaceutical compounds if, 0.5 < Pa < 0.7 and the probability is less and the compound is likely to reveal their mode of action in the studies.
- The compound must be a new chemical entity if Pa < 0.5, and the compound is unlikely to reveal its activity in the test groups.

We have not considered the activity profile (Po) less than 0.7 so as to minimize confusions. Thus, in planning experiments and choosing the activities on which the compound has to be tested, one should have in mind the necessity of balancing between the novelty of pharmacological action and the risk to obtain negative results in the experimental testing. Surely, one will likewise consider the specific interests for certain sorts of action, trial facilities, and more PASS can be utilized for the forecast of the biological active spectrum for the identified and new formulated compounds.

In our analysis, we have seen the potential activity of a single drug "Patentiflorin-A" from *Justicia gendarussa*. Even though, it is not the conclusion of a crude plant decoction, the single drug "Patentiflorin-A" would prove to cure various ailments. But the so called anti-HIV nature of this drug is not predicted in our research. Patentiflorin-A is predicted to be antagonistic against the treatment of various ailments. The list of ailments and their possibilities are sketched in Figure 2.

Alzheimer and various other diseases

Patentiflorin-A is actually an antagonist to a variety of diseases such as Leishmaniasis, Alzheimer's disease, Huntington disease, Parkinson disease treatment, Gaucher disease treatment, Anti-allergic, Charcot-Marie-tooth disease treatment, etc. (Hu-Nan and Yao, 1978; Duke and Ayensu, 1985; Chopra *et al*., 1986).

Anti-microbial

Patentiflorin-A is a potent Anti-microbial and antibiotic agent. It is predicted to be anti-bacterial (*Bacillus subtilis* and *Staphylococcus epidermidis*), antiprotozoal (especially *Plasmodium antagonist*), anti-viral (especially in Influenza Treatment), anti-mycoplasmal, antifungal, anticonvulsants and also treats common cold and cough. It also protect lung and stops lungs infection such as idiopathic pulmonary fibrosis. It is also predicted to be involved in the treatment against eye disorders, cataract and concomitant medication. It is also predicted to be useful in diagnosing certain pathogenic infections and highly as an anxiolytic agent.

Immunomodulant

Patentiflorin-A is also an immunomodulant and

stabilizes transplantation of organs. It also helps in the treatment of psoriasis and scleroderma. It is also a potent anti-allergic and anti-inflammatory substance (Sawatzky *et al.,* 2006; Sridhar *et al*., 2006). It is also an immune booster and helps in wound healing.

Hepatoprotective

It is also involved in the protection of liver from damage, it cures jaundice and cirrhosis of the liver and hence a hepatoprotective.

Cardioprotective

It is also used as a cure for various lifestyle diseases like diabetes, hyperglycemia, myocardial infarction etc. It is also a potent anti-aging, anti-clot (cardio vascular) bioconstituent used for cardiac valve treatment, obesity and hypertension treatment, clearing atherosclerosis and hence it is cardio protective. It also helps in the regulation of hormones, relieves pain and suppresses muscle spasms. It helps in rheumatoid arthritis treatment also (Paval *et al*., 2009).

Neurotonic

It is also predicted to be involved in the psychometric treatment like Attention Deficit Hyperactivity Disorder (ADHD), anti-anesthetic, antidepressants and neuropathological treatment cum memory booster.

Gastro-protective

It is also predicted to be used in the treatment of gastrointestinal and hepatic pathology, with hypoglycemia coagulopathy and protein-losing enteropathy, etc., It helps in protein metabolism, peptic ulcer and stomach treatment (Duke and Ayensu, 1985).

Anti-cancerous

Patentiflorin is predicted that it could prevent cancer especially neoplasma (tumor) and metastatic colon cancer, anti-toxicity especially against xenobiotic, destroys cancer cells, antioxidant, useful in the treatments of lung cancer, breast cancer, colorectal cancer, colon cancer, Nnn-hodgkin's lymphoma (cancer), lymphoma cancer, blood cancer and cervical cancer treatment and helps to identify cancer cells in radiotheraphy and chemotherapy. In breast cancer treatment it also helps in apotopsis of the cells (Figure 3). Out of 132 properties, 57 accounts for the anti-cancerous property and thus patentiflorin is proposed to be a great drug for cancer treatment.

Energizer and beautifier

To add to this, it is also used for beauty treatment as it deletes melanin, and gives glow to the body because of being a health tonic and an energy booster.

Plant growth modulator

To add to our astonishment, it also helps plants on the biological control of insects, microspore maturation in plants, anti- weed growth and as a suppressant. The phytochemical compound present in the *J. gendarussa* leaf extracts were flavonoids, apigenin and vitexin. Moreover, alkaloids, reducing sugar, sitosterols and many unidentified sterols were also present in *J. gendarussa*. Reduced oxidative stress and forestalling of inflammatory factors expression was also reported by Wahi *et al*. (1974) which was due to apigenin Sridhar *et al*. (2006) reported that vitexin inhibits the 5-lipoxygenase pathway which in addition to COX-2 pathway is vital in the process of anti-inflammatory caused by this flavonoid.

Ethno botanically speaking, the leaf is antispasmodic, carminative (Hu-Nan and Yao, 1978) and has antiperiodic properties (Duke and Ayensu, 1985). The leaves and tender young shoots are diaphoretic (Chopra *et al*., 1986). A decoction is used in the treatment of chronic rheumatism (Chopra *et al*., 1986).

An infusion of the leaves is taken internally in the treatment of pains in the head, paralysis of one side of the body and facial paralysis (Chopra *et al*., 1986). The leaf juice is used in the treatment of earache (Chopra *et al*., 1986). The bitter root is anodyne, diaphoretic, diuretic and laxative (218). The root bark is

emetic (Duke and Ayensu, 1985). The whole plant is emetic and febrifuge (Chopra *et al*., 1986). A decoction is used to treat bruises (Duke and Ayensu, 1985). The chemical properties available for the "Patentiflorin-A" in pubchem compound database confirms the stability of the compound and so could be tested for the biological activity.

CONCLUSION

From the *in silico* studies, it is hence predicted that Patentiflorin-A is a potent cardioprotective, hepatoprotective, anti-microbial, anti-fungal, anti-viral, anti-protozoal, immune modulant, memory booster, neurotonic, gastroprotective, energizer, beautifier and plant growth modulator. It could cure various diseases such as Alzheimer's disease, Parkinson's disease, Gaucher disease, Charcot-Marie-tooth disease, etc.

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