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Admet Study of Phytochemicals Used In Autoimmune Disease

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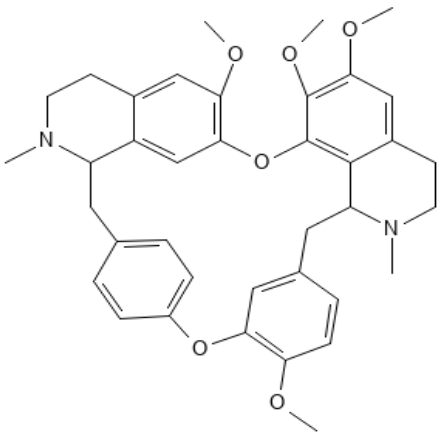
Abstract
Autoimmune disease is a complex term, which describes immune system attacks as a breakdown of tolerance to auto reactive immune cells. It is associated with genetic, infectious,environmental predisposing factor.The use of herbal medicines in autoimmune significantly act on immune system and improves them. Tetrandrine (Tet), a bis-benzylisoquinoline alkaloid isolated from the creeper *Stephania tetrandra S Moore*, belong to family Menispermacae has been used for decades in Mainland China to treat patients autoimmune illnesses rheumatism. Punarnavine, alkaloid obtained from *Boerhavia diffusa* belong to familyNyctaginaceae. Punarnavine significantly reduced the LPS induced elevated levels of proinflammatory cytokines such as TNF-α, IL-1β, and IL-6 in mice. This review summarizes ADMET Study of tetrandrine and punarnavine by software analysis SWISS ADME and ADME2.0 and determine drug likeliness.(1)

Keywords
Tetrandrine,Punarnavine,immunomodulator,Lipophilicity,Lipinski Rule, AMES toxicity

1. Introduction

1.1 TETRANDRINE-
Tetrandrine, is a bis-benzylisoquinoline alkaloid.
BIOLOGICAL SOURCE AND FAMILY-It is obtained from Creeper of *Stephania tetrandra S Moore*,belonging to family menispermaceae
GEOGRAPHICAL SOURCE-It is native to mainland china and taiwan,jiangxi,haina
CHEMICAL CONSTITUENTS- It contain alkaloids,isoquinoline alkaloids, fangchinoline (0.5%), cyclanoline (0.1%) and dimethyltetrandrine iodide (muscle relaxant) other chemicals are dimethyltetrandrine iodide, cyclanoline, menisine, menisidine, oxofangchirine, stephenanthrine, stepholidine and bisbenzylisoquinoline. Fenfangjines F, G, H, and I.
STRUCTURE-



It contains quinoline ring which is responsible for potent immunomodulator,anticancer,antiestrogenic activity. (2)

MECHANISM OF ACTION

TETRANDRINE CAUSES DOWNREGULATION OF PROTEIN KINASE-C,INTERLEUKIN-2 SECRETION, T-LYMPHOCYTE

↓

TETRANDRINE INHIBITS PHOBOL 12-MYRISTATE 13-ACETATE

↓

IT INHIBIT NEUTOPHIL-MONOCYTE CHEMOTACTIC FACTOR-1 UPREGULATION HENCE REDUCED PRODUCTION OF OXYGEN FREE RADICAL OXYGEN, DOWN-REGULATED SYNTHESIS AND RELEASE OF SOME PRO-INFLAMMATORY CYTOKINES

↓

USED AS ANTIRHEUMATIC DRUG

1.2 PUNARNAVINE

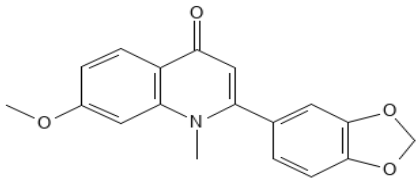
Punarnavine,it is a herbaceous plant and Punar means -once again, nava means - becoming new. This is also known as 'Spider lings' as this plant grows low and spreads like spider.

BIOLOGICAL SOURCE- It is obtained from*Boerhavia diffusa*,belong to family Nyctaginaceae

GEOGRAPHICAL SOURCE- It is native plant found in Africa,Asia,South america,carribean,South america,south asia.

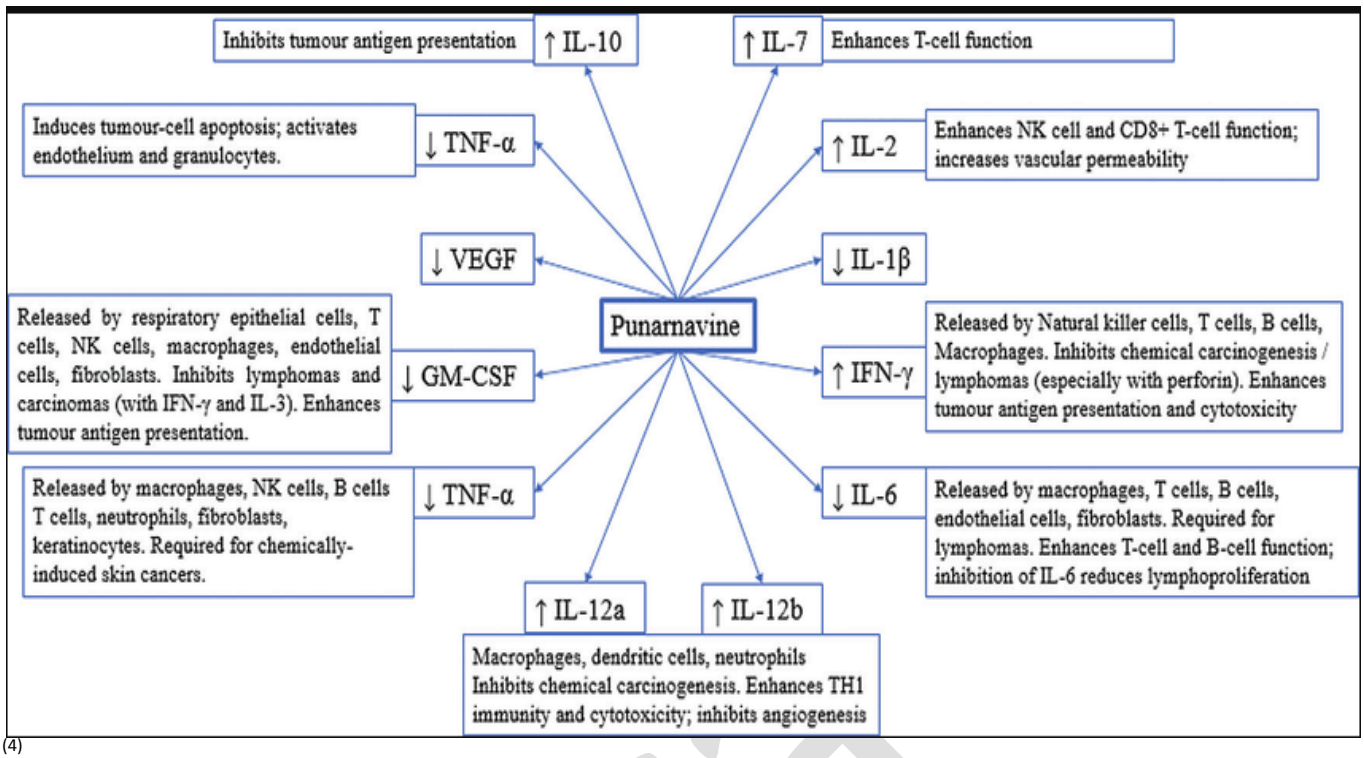
CHEMICAL CONSTITUENTS-Boerhaavia G and Boerhavia H are two rotenoids isolated from *B. diffusa*. A quinolone alkaloid, lunamarine, isolated from *B. diffusa* has shown some *in vitro* anticancerantiestrogenic immunomodulatory and anti-amoebic activity. The plant contains a protein called BDP-30, presumably a ribosome-inactivating protein. [3]

STRUCTURE-



It is a quinoline alkaloid having immunomodulatory, antiestrogenic,antiinflammatory activity.

MECHANISM OF ACTION-



(4)

2. Materials And Methods

2.1 DATABASE SCREENING FOR COMPOUND SELECTION-

1. SWISS ADME-It is a free web tool which is used to determine drug likeliness, pharmacokinetics,medicinal chemistry of molecules. It is a simple and accurate method to understand ADME properties.
2. ADME2.0 – It is the enhanced version of ADMET and involves evaluation and batch screening which allow calculation of 88 ADMET-related including 17 physicochemical properties,13 medicinal chemistry properties.
3. PUBCHEM-It is a database of chemical molecules and its online canonical smiles were obtained. These smiles were put in SWISS ADME and ADME2.0 and the data was reported.

SMILES OF TETRANDRINE-
COc1ccc2cc1Oc1ccc(cc1)CC1c3cc(c(OC)cc3CCN1C)Oc1c(OC)c(OC)cc3c1C(C2)N(C)CC3
SMILES OF PUNARNAVINE- COc1ccc2c(=O)cc(-c3ccc4c(c3)OCO4)n(C)c2c1 (5)

3. Screening of Compounds from Database

3.1 ABSORPTION

Absorption is a process by which a drug molecules reaches to its site of administration.
Bioavailability is defined as the fraction of drug administered reaching to systemic circulation.
As per ADME2.O data, tetrandrine doesn't follow lipinski rule [rule of 5],hence it has poor absorption and permeability. Punarnavine follows lipinski rule [rule of 5] it has more absorption,more permeability,ultimately highest bioavailability.
As per SWISS ADME, both drugs tetrandrine and punarnavine, it has more absorption,more permeability and highest Bioavailabilty.
The bioavailability score of tetrandrine and punarnavine Is 0.55,0.55. (6)

3.2-DISTRIBUTION

Distribution is a process by which a drug molecule gets transfer from one compartment to another.
Lower the LOG P higher is the lipophilicity.

As per the SWISS ADME, LOG P OF TETRANDRINEis 4.87 and PUNARNAVINE is 3.14, which signify that the drugs are highly lipophilic and permeability to reach target tissue is highest.
Hence it also signifies that punarnavine and tetrandrine has optimal lipophilicity and cross BBB[BLOOD BRAIN BARRIER]
As per the ADME2.0, the **volume of distribution[V_D]** Of TETRANDRINE and PUNARNAVINE is 0.929 and 0.843. The BBB penetration of tetrandrine and punarnavine score is 0.287 and 0.575.
Skin permeation [logKp] of tetrandrine is highest than punarnavine due to highest perfusion rate and lipophilicity.
Higher the LOG P more is the **solubility**[LOG S];hence tetrandrine has highest solubility compare to other compounds.
Tetrandrine has highest solubility than punarnavine.
Plasma protein binding[PPB] is amount of drug binds to plasma protein, which increases duration of action and drug extensively bound to plasma protein tend to have low therapeutic index.

The tetrandrine PPB Score is 71.77% and punarnavine is 97.09% hence,punarnavine is extensively bound to Plasma protein and have low therapeutic index. [7]

3.3 METABOLISM

As per both the softwares;

Enzymes	ADME2.0	SWISS ADME
CYP1A2 INHIBITOR	tetrandrine and punarnavine inhibits enzyme.	tetrandrine and punarnavine inhibits enzyme.
CYP2C19 INHIBITOR	tetrandrine and punarnavine doesn't inhibits enzyme.	tetrandrine and punarnavine doesn't inhibits enzyme.
CYP3A4 INHIBITOR	Punarnavine inhibit enzymetetrandrine doesn't inhibits enzyme.	Punarnavine inhibit enzymetetrandrine doesn't inhibits enzyme.
CYP2D6 INHIBITOR	Punarnavine inhibit enzyme tetrandrine doesn't inhibits enzyme.	Punarnavine inhibit enzyme tetrandrine doesn't inhibits enzyme.

3.4 EXCRETION

THE IDEAL VALUE OF CLEARANCE IS
High: >15 mL/min/kg
Moderate: 5-15 mL/min/kg
Low:<5ml/min/kg

COMPOUND	**CLERANCE**	**$T_{1/2}$**
TETRANDRINE	9.019	0.18
PUNARNAVINE	9.583	0.186

Tetrandrine and punarnavine has moderate clearance and have short half lives. [8]

3.5 TOXICITY-

The AMES test[Salmonellatyphimurium reverse mutation assay] is the test to identify revert mutation which are present in strains by testing its capacity to revert mutation present in a mutant bacteria and restore its ability to synthesize an essential amino acid required for growth.
If the test is positive it indicates that the given chemical is mutagenic.
If it is category 1 then AMES positive and Category 0 than AMES negative

COMPOUND	AMES TOXICITY
TETRANDRINE	0.084
PUNARNAVINE	0.936

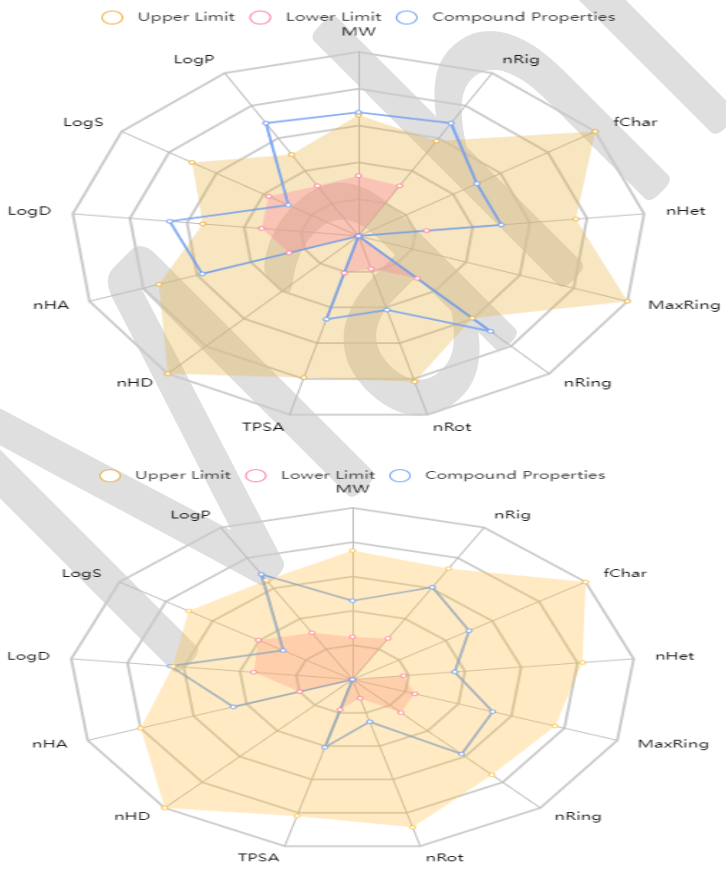
4. COMPARATIVE DATA ANALYSIS BY ADME2.0 AND SWISS ADME-

compound	No. of hydrogen bond donors	No. of hydrogen bond acceptors	LOG P	LOG S	LIPINSKI RULE	PFIZER SCORE	BBB PENETRATION	AMES TOXICITY
TETRANDRINE	0	8	5.994	-5.145	REJECTED	REJECTED	0.287	POSITIVE
PUNARNAVINE	0	5	3.331	-5.559	ACCEPTED	REJECTED	0.575	NEGATIVE

TABLE 1-ADMET analysis by ADME2.0 Software [9]

Compound	No. of hydrogen bond donors	No. of hydrogen bond acceptors	LOG P	LOGS	lipinski rule	GI absorption	Bioavailabilityscore	Skin permeation
Tetrandrine	0	8	4.87	-8.02	yes	high	0.55	-5.37
Punarnavine	0	4	3.14	-4.11	yes	high	0.55	-5.97

TABLE-2-ADMET analysis by SWISS ADME software [10]



SOFTWARE REPRESENTATION OF ALL PARAMETERS OF TETRANDRINE AND PUNARNAVINE BY ADME2.0

Conclusion

Tetrandrine and Punarnavine are novel drugs for autoimmune disorder,both the drugs have optimal absorption,perfusion rate,permeability and bioavailability.it has optimal lipophilicity and crosses BBB,it has high solubility and punaravine,extensively bound to plasma protein retards the distribution rate,it acts inhibitory effect on metabolism,which potentiate drug action.these drug has moderate clearance and short half lives and it accepts lipinski rule and show drug likeliness and less toxic.

Through this study it conclude that by software analysis Tetrandrine and punarnavine are safe, effective and best immunomodulator against various autoimmune disease.[(11)]

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