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IN-SILICO EVALUATION OF *KAPITTHA PATRA* (LEAVES OF *FERONIA LIMONIA*) IN HEPATITIS B AND ITS MOLECULAR ASSESSMENT

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ABSTRACT

Background: Cirrhosis, hepatocellular carcinoma, and chronic hepatitis are all linked to hepatitis B virus (HBV) infection, which continues to be a serious global health concern. Antiviral treatments are available, however long-term use is linked to side effects and medication resistance. Though their molecular mechanism against HBV is yet unknown, *Feronia limonia* leaves (*Kapittha patra*), which have long been employed in traditional medicine for liver problems, have hepatoprotective effect. The current study used network pharmacology and molecular docking techniques to assess the possible protective effect of *Feronia limonia* leaves against Hepatitis B.

Methods: IMPPAT and Dr. Duke's databases were used to gather phytochemicals associated with *Feronia limonia* leaves. ADMETlab 3.0 was used for ADMET screening, and SwissTargetPrediction was used for target prediction. GeneCards and the Human Protein Atlas databases provided targets associated with hepatitis B. Venny 2.1.0 was used to identify common targets, and Cytoscape and STRING were used to analyze protein–protein interactions. DAVID Bioinformatics resources were used to perform KEGG pathway enrichment. PyRx was used to perform molecular docking on certain phytochemicals, and Discovery Studio was used to show the results.

Result: 20 of the 72 phytochemicals found met ADMET requirements. Hepatitis B and phytochemicals were shown to have 36 targets in total. STAT3, EGFR, TNF, ALB, MMP9, SRC, AKT1, and BCL2 were among the hub targets. Significant enrichment in the "Pathways in Cancer" and "Hepatitis B" pathways was found by KEGG analysis. Psoralen, spathulenol, and myristicin showed good binding affinities for HBV-related targets, especially STAT3, according to molecular docking. The strongest binding affinity against STAT3 was shown by psoralen (−7.9 kcal/mol).

Conclusion: *Feronia limonia* leaves may have anti-Hepatitis B properties by modifying viral and inflammatory signaling pathways that involve TNF and STAT3. These results call for more experimental and clinical confirmation and offer scientific backing for the traditional usage of *Kapittha* in liver problems.

Keywords: *Kapittha*, Hepatitis B, Computational pharmacology, Molecular docking

INTRODUCTION:

The hepatitis B virus (HBV), a partly double-stranded DNA virus that is a member of the Hepadnaviridae family, is the cause of hepatitis B, a serious worldwide health issue. Exposure to contaminated blood and bodily fluids, including perinatal transfer, hazardous injections, sexual intercourse, and tainted medical procedures, is the main way the infection spreads. Hepatocellular carcinoma, liver cirrhosis, and acute or chronic hepatitis can all result from HBV infection. More than 240 million people worldwide suffer from chronic HBV infection, especially in Asia and sub-Saharan Africa where prevalence is still high. It is believed that almost two billion people have contracted the virus **[1]**. Antiviral medications such interferon-α, pegylated interferon, lamivudine, entecavir, and tenofovir are the mainstay of current treatment approaches since they inhibit viral replication and slow the course of illness. These treatments do, however, have a number of drawbacks and side effects. While long-term nucleos(t)ide analogue therapy may cause nephrotoxicity, bone mineral loss, mitochondrial toxicity, and the development of viral resistance in certain situations, interferon-based therapies are linked to flu-like symptoms, weariness, depression, and hematological abnormalities. Therefore, safer and more successful therapeutic techniques are still required for the long-term care of hepatitis B infection, even with the availability of potent antiviral medications **[2]**.

Kapittha patra (*Feronia limonia* leaf) is having properties such as *Atisarahara* (Anti-diarrhoeal) and *Chardighna* (Anti-emetic), **[3]** although there is no direct reference for the antagonist activity towards hepatitis, the researches in *Kapittha patra* indicated that

via lowering increased liver enzyme levels and oxidative stress indicators, the ethyl acetate and aqueous fractions of *Feronia limonia* leaf exhibited strong hepatoprotective effect against carbon tetrachloride-induced liver damage. Additionally, the fractions showed minimal cytotoxicity, suggesting relative safety at the quantities under evaluation. It is concluded that *Feronia limonia* leaves may be used as a natural treatment for liver diseases and have promising hepatoprotective potential, perhaps because of their antioxidant phytoconstituents **[4]**.

Here the role of *Kapittha patra* also plays a role due to its use in folklore practice in villages of Belagavi in Karnataka **[5]**. With these evidences, evaluation of *Kapittha patra* through network pharmacology will help in knowing the mode of action and will help us in identifying whether the folklore practice is valid or not.

MATERIALS AND METHODS:

Ethical statement:

As the study doesn't have any involvement of human or animal participants in it the study is don't require permission from Institutional Ethical Committee or Institutional Animal Ethical Committee.

Collection of phytochemicals and targets related to the chemicals:

Two databases namely IMPPAT and Dr. Dukes were used to collect the phytochemicals related to the plant with the part specific **[6, 7]**. Further the SMILES (Simplified Molecular Input Line Entry System) of the listed phytochemicals were collected, later the SMILES were uploaded in ADMET Lab 3.0 for the assessment of Absorption, Distribution, Metabolism, Excretion and Toxicity **[8]**. Followed by that based on the evaluation, each SMILES are uploaded into Swiss Target Prediction for procurement of targets related to each phytochemical **[9]**.

Acquiring disease targets and common targets:

The disease for which the plant needs to be evaluated is chosen followed by that the disease related targets are obtained from HPA (Human Protein Atlas) and Genecards **[10, 11]**. Based on the relevance score the targets in the genecard database is filtered and the duplicates in both the database is removed. Followed by that the targets related to plant phytochemicals and the targets related to disease are uploaded into Venny 2.1.0 for getting the overlapping targets **[12]**.

Protein interaction and Hub gene prediction:

The overlapping targets are uploaded into STRING 12.0 for assessing the interaction between each of the target **[13]**. Moreover, the targets were uploaded into Cytoscape 3.10.4 for predicting the top 10 targets among the common targets **[14]**. Cytohubba

was used for prediction of top 10 gene targets **[15]**.

KEGG pathway prediction:

With the overlapping targets, the Kyoto Encyclopedia of Genes and Genomes (KEGG) pathway prediction was done in DAVID Bioinformatics **[16]**. The targets were uploaded and the pathways related to targets are obtained and the top 10 pathways are considered on the basis of gene count.

Topological analysis:

The targets, chemicals and pathways are segregated and they are made to merge to form a network and further the topological analysis is performed. Edge betweenness and degree layout is assessed for knowing the which phytochemicals and targets that can be considered for molecular docking.

Molecular docking:

The 3D structure of the ligand is obtained from Pub Chem and the target related structure is obtained from RCSB PDB **[17]**. The hetero atoms and the water molecules were removed from the target further polar hydrogen bond, kollmann charges were added to the target. Using PyRx software the ligands are uploaded with a force field of uuff and mmff94 after energy reduction **[18]**. Followed by that targets are uploaded into PyRx for docking and checking binding affinity score. With Discovery studio 2025 the 2D and 3D visualization of the docking is done **[19]**.

RESULTS:

Acquiring targets related to Phytochemicals:

In IMPPAT there was 72 phytochemicals related to '*Feronia limonia*' with the used part as leaf, in Dr. Dukes there were no phytochemicals related to the plant. Further the SMILES related to the phytochemicals were obtained, on total 63 SMILES were obtained. Upon assessing the ADMET parameters such as Drug likeliness with a score of greater than 0.67, Lipinski as 0 or 1, Human intestinal Absorption (HIA) within 0.0 to 0.5 as cut off and Hepatotoxicity as 0.0 to 0.5, a total of 20 phytochemicals related to the plants were obtained. By uploading the individual SMILES into Swiss Target Prediction the targets related to the phytochemicals were obtained.

Overlapping targets:

From Gene cards after applying the cutoff relevance score as 7, a total 216 targets related to "Hepatitis B" was obtained and in HPA 141 targets were found. Followed by removing the duplicates a total of 349 targets related to Hepatitis B was obtained, these targets were uploaded into Venny 2.1.0 and the targets related to plants i.e. 574 targets were also uploaded. After these steps 36 common targets were obtained from both the disease and the phytochemical target. **Figure 1** depicts the common targets between *Kapittha* and Hepatitis B.

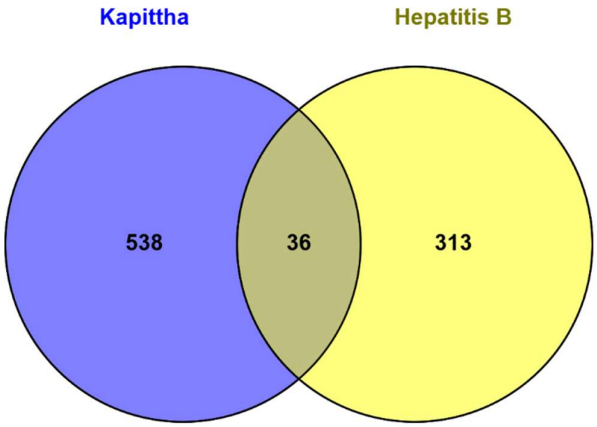

Figure 1: Overlapping targets between *Feronia limonia* and Hepatitis B

PPI and top 10 targets:

With STRING 12.0, the common targets were uploaded and the species was given as *Homo sapiens*, the interaction between the 36 targets was observed. Among the 36 common targets the top 10 targets were predicted based on the shortest path, and the top 10 gen targets were STAT3, EGFR, TNF, ALB, MMP9, SRC, NFKB7, AKT1 and BCL2. The Protein interaction is shown in the **Figure 2**.

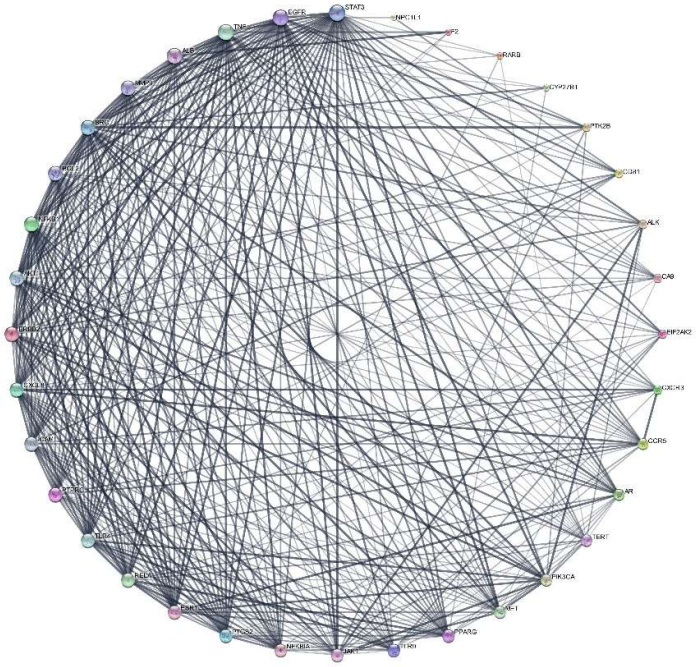

Figure 2: PPI of the common targets

KEGG pathway prediction:

With the 36 common targets the pathway prediction was done, a total of 122 pathways were obtained. Among this 'Pathways in Cancer' was having highest gene count with a number of 21. Followed by that 'Hepatitis B' pathway was having 14 targets in them.

'Hepatitis C' was also in the top 10 pathways.

Topological analysis:

36 targets, 10 pathways and 19 phytochemicals were uploaded into Cytoscape 3.10.4 and the network between the target, pathway and chemicals was constructed. Based on the degree layout and edge betweenness, Spathulenol had the highest degree layout and edge betweenness, Eucalyptol had the lowest edge-betweenness and degree layout. Among the targets

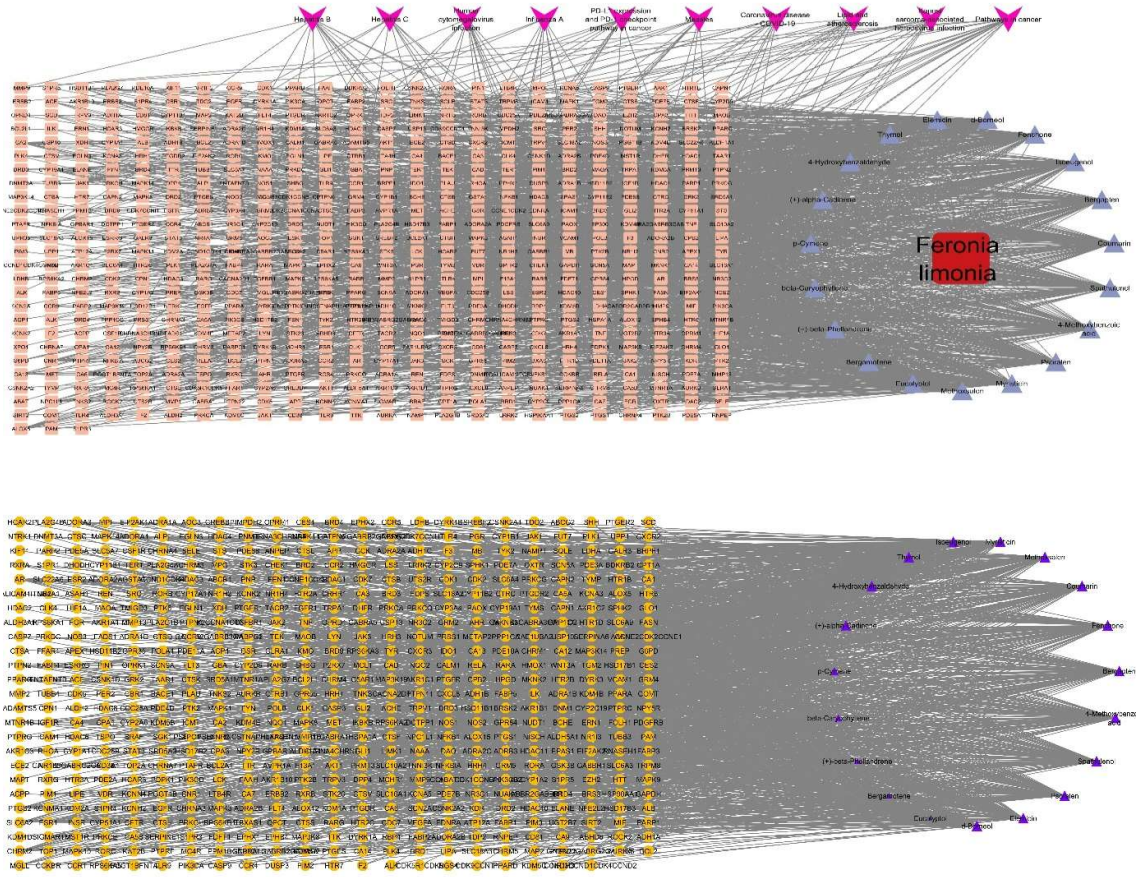

Figure 3: Topological analysis of *Feronia limonia* leaves

Molecular docking:

The targets STAT3, TNF and EGFR were chosen for docking with the chemicals spathulenol, psoralen and myristicin. Among this psoralen had the highest binding affinity towards STAT3, while Myristicin towards TNF had the lowest binding affinity of -4.9 kcal/mol, although the average binding affinity was high in terms of spathulenol when compared to other two phytochemicals. All three phytochemicals had shown their individual highest binding affinity towards the target STAT3. **Figure 4** depicts the 3D and 2D structure of the psoralen towards STAT3 target.

Phytochemical	Binding affinity of targets and Phytochemicals (kcal/mol)			
	Targets	TNF	EGFR	STAT3
	PDB ID	2tnf	2gs60	6njs
Spathulenol		-5.5	-6.7	-7.8
Myristicin		-4.9	-5.6	-6.5
Psoralen		-5.3	-6.7	-7.9

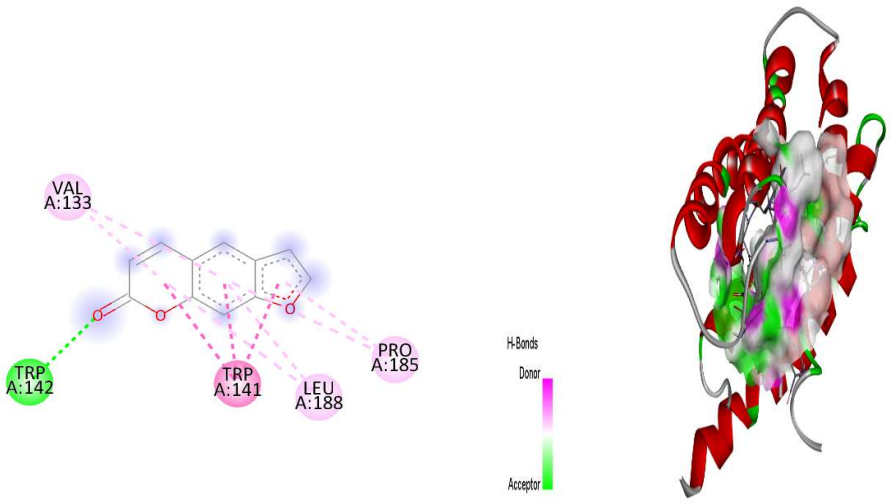

Figure 4: Docking 2D and 3D visualisation of Psoralen towards STAT3

DISCUSSION:

The plant *Kapittha* (*Feronia limonia*) is having properties such as *Katu rasa*, *Katu vipaka* and *Ushna virya*, although the Ayurvedic pharmacological principles don't have enough evidence in supporting the claim that the plant can be used for Hepatitis B, the folklore practitioners are using the plant in liver related conditions either as a single drug or else in a combination. Though the mode of action is unclear, the hepatoprotective activity of the plant is proven by the previous researches. Hence, while performing the computational pharmacology there were few phytochemicals such as psoralen, myristicin and spathulenol has activity towards the targets related to the Hepatitis B such as TNF, STAT3. Few important pathways such as, Hepatitis B and Pathways in cancer has also involved in the prediction of pathways.

In experimental studies, myristicin, a naturally occurring substance primarily found in nutmeg, has been shown to lessen liver damage and inhibit inflammatory mediators like TNF-α. Myristicin dramatically decreased high ALT and AST liver tests and shielded hepatocytes from inflammatory damage, according to animal studies **[20]**.

In experiments, psoralen, a bioactive furanocoumarin extracted from *Psoralea*

corylifolia, has shown encouraging anti-Hepatitis B action. Psoralen can prevent HBV DNA replication and decrease the release of viral antigens including HBsAg and HBeAg in HepG2.2.15 cell lines, according to in vitro studies. Additionally, the substance is said to have hepatoprotective, immunomodulatory, and antioxidant qualities that may help reduce oxidative stress and liver inflammation brought on by HBV. It is thought that its antiviral activity involves interfering with viral replication pathways and suppressing HBV transcription. Despite these promising results, preclinical research makes up the majority of the evidence, and clinical confirmation is still absent. Furthermore, a thorough assessment of its safety profile is required due to worries about phototoxicity and dose-dependent hepatotoxicity **[21]**.

One important pro-inflammatory cytokine that is essential to the pathophysiology and immune response of Hepatitis B virus (HBV) infection is tumor necrosis factor-alpha (TNF-α). In response to HBV infection, macrophages, T cells, and Kupffer cells primarily release TNF-α, which aids in both viral removal and liver damage. By triggering intracellular antiviral pathways and encouraging the death of infected hepatocytes, it aids in the suppression of HBV replication. On the other hand, persistent hepatic inflammation, cirrhosis, fibrosis, hepatocyte necrosis, and the development of hepatocellular carcinoma might result from excessive or chronic TNF-α production. Patients with chronic hepatitis B frequently have elevated TNF-α levels, which are linked to the severity of the illness **[22]**.

An essential transcription factor in the development and pathophysiology of Hepatitis B virus (HBV) infection is signal transducer and activator of transcription 3 (STAT3). Increased viral persistence, hepatocyte survival, inflammation, and immune evasion can result from HBV proteins, especially HBx protein, activating the STAT3 signaling pathway. In patients with HBV infection, persistent activation of STAT3 is linked to cirrhosis, fibrosis, chronic liver inflammation, and the development of hepatocellular carcinoma (HCC). Additionally, STAT3 promotes HBV-related liver carcinogenesis by controlling the expression of genes linked to angiogenesis, cell proliferation, and anti-apoptotic processes. STAT3 is regarded as a viable molecular target for the development of anti-HBV and anti-cancer treatments because of its crucial role in HBV replication and the advancement of liver disease **[23]**.

Viral entrance, replication, immunological response, chronic inflammation, and the development of cirrhosis, hepatocellular cancer, and liver fibrosis are all part of the Hepatitis B virus (HBV) pathway. Through

the sodium taurocholate co-transporting polypeptide (NTCP) receptor, HBV penetrates hepatocytes and releases its partly double-stranded DNA into the nucleus, where it forms covalently closed circular DNA (cccDNA), which acts as a template for viral replication. Numerous host signaling pathways, including NF-κB, JAK/STAT, PI3K/Akt, MAPK, and Wnt/β-catenin pathways, are activated by HBV proteins, especially HBx. This promotes viral persistence, inflammation, hepatocyte proliferation, and suppression of apoptosis. Carcinogenesis, fibrosis, and oxidative stress are all influenced by the long-term activation of inflammatory cytokines such as TNF-α, IL-6, and TGF-β. Long-term HBV infection raises the risk of hepatocellular cancer and eventually causes immune-mediated liver damage **[24]**.

Thus, the phytochemicals that had degree layout and edge betweenness, had been taken for docking and further those phytochemicals had shown good number of binding affinities towards the target, especially the psoralen had shown highest binding affinity towards STAT3, while visualising in the 2D structure it had shown conventional hydrogen bonding with the target. Furthermore, the previous studies on psoralen had also given us an idea that the phytochemical does have certain action on hepatic cell line. With all these evidences we can assume the mode of action of *Kapittha* leaves in Hepatitis B.

Although the study has given probable mode of action, still the study lacks in few points especially the study solely relies on the databases which gets updated regularly, thus a Liquid Chromatography – Mass Spectroscopy followed by that in-silico study will give further more validation for the study. Nevertheless, the final proof will be reliable only with the clinical study followed by an in-vivo study is done.

CONCLUSION:

Ayurveda is a science where plants play a major role in treating all the disease, although many plants have been registered in classical texts there are still many plants that are to be registered so as to know their other possible pharmacological actions. One among the plant is *Feronia limonia* , although the leaves are used by folklore practitioners, still the plant's mode of action is unclear. Thus, by performing computational pharmacology, we probably predicted the mode of action of the plant. The study has not only validated the traditional practice but also helped us in exploring new horizons of the plant.

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CONFLICT OF INTEREST: Nil

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