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Cocculus hirsutus (L.): Conventional uses, phytochemistry, pharmacological actions and clinical studies

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Abstract

A member of the Menispermaceae family, *Cocculus hirsutus* (L.) is a perennial climbing plant primarily found in equatorial and semitropical climates. The dominant objective of this article is to consolidate as well as evaluate the empirical evidence pertaining to the conventional uses of herbal plants for treatment, and to determine how the bioactive chemical components found in these plants contribute to their pharmacological effects. Everything we know about this plant comes from internet databases, including Medline, PubMed, SciFinder, Google Scholar, and Scopus connections, as well as some secondary sources such as books and proceedings. Different plant parts are used in the medical care of various illnesses, such as fever, skin conditions, urinary disorders, and digestive issues. Alkaloids like jasminotine and hirsutine, along with their derivatives and other classes of chemical compounds including flavonoids, terpenoids, and volatile compounds, have been discovered in whole or in their entirety. The plant extract is tested for a variety of psychopharmacological effects, including antibacterial, antidiabetic, hepatoprotective, and immunomodulatory properties. Various activities are depicted in the following Figure. There have been few studies conducted on the chemical elements of this plant, despite its significant role in treating many diseases. *In vitro* methods were typically used to conduct biological experiments, with only a few involving the use of animals. The pharmacological effects of the plant extract must be evaluated through numerous, well-designed *in vivo* and clinical studies before it can be considered for future development.

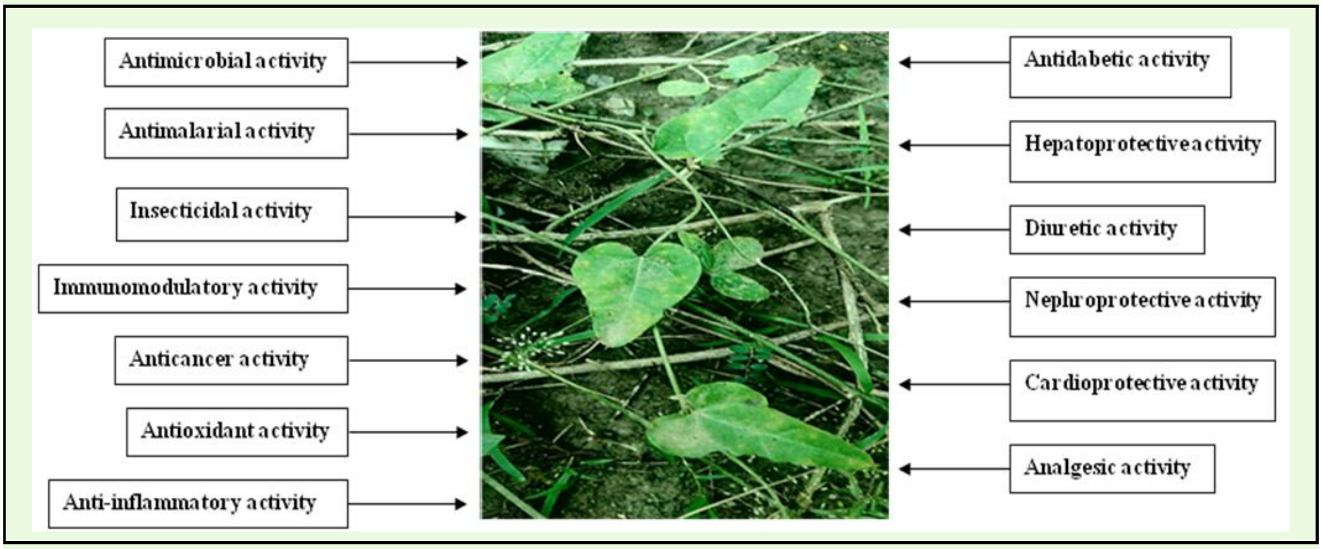

Figure: Pharmacological activities of *C. hirsutus*.

1. Introduction

A family of over 500 plant species called Menispermaceae includes about 70 genera. Ten further species make up the genus, and they are found in Asia, Africa, Australia, and Western Hemisphere (Wet *et al.*, 2015) they are *Cebatha hirsute* (L.) Kuntze, *Cebatha villos, Cocculus hastatus* DC, *Cocculus aristolochiae* DC, *Holopeira-torrida cocculus* R.L. Massey and Broun, Kurz*: Cocculus linnaeanus* Colebr., *Cocculus sepium, Menispermum hirsutum* (L.) and *Cocculus villosus* DC (Logesh *et al.*, 2020).The clear image of this plant is depicted in Figure 1. These different plant varieties are hinge in abundance in equatorial and semi-tropical regions. These are distributed throughout Asia, *i.e.,* in Pakistan, India, Myanmar, and Nepal. They also exist

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in southern China as well as in Africa, Egypt, Sudan, Eritrea, Angola, south-western and southern Africa (Shrestha *et al.*, 2018). Broom creeper is the popular name for *C. hirsutus* in English, Huyer is for Bengali, Farid Buti is for Urdu, Jamti ki bel is for Hindi, Kaage mari is for Kannada, Paatalgarudakkoti is for Malayalam, Patalagarudi is for Sanskrit and Chipuru-tiga is for Telugu (Panda *et al.*, 2007). In a region like South Asia, various portions of this plant are frequently used to treat rheumatism, skin conditions, fever, congenital diseases and as a detoxification agent. In Africa, berries are proned as food and as a dye; while stems are used for making baskets and the Tsonga people routinely include these plants in their diet (Chadha *et al.*, 1950). The plant extracts demonstrate diuretic, analgesic, laxative, and anti-inflammatory properties; alkaloids and other chemicals have also been spotted in the plant and other plant parts.

47 million instances of pandemic disease Coronavirus 2019 (COVID-19) were reported in November 2020, spanning 216 countries and territories (Rufaida *et al.*, 2021). Many research studies are utilising plant derivatives as natural products, as ingredients for facilitating the evolution of vaccines and antiviral medications. According to the Clinical Trials Registry of India, an investigation into the productiveness and protection of an aqueous extract of *C. hirsutus* to treat Coronavirus infection has begun in India. A randomised, phase-I, placebo-controlled and dose-escalation research was registered to evaluate safety and adequacy of tablets made from aqueous extract in healthy adult humans. It is crucial for assessing and comprehending the scientific data regarding the chemical components and pharmacological properties of the plants that have historically been utilised to create therapeutic pharmaceuticals for various ailments. Since *C. hirsutus* outcomes have been reported, this review focuses on consolidation and investigation of scientific data related to those results.

Figure 1: *C. hirsutus* plant.

1.1 Traditional uses

- For a cooling effect, the paste of leaves had been applied to the head and plant extract juice combined with sesame oil was used to reduce heat. Applying plant mush to the umbilicus can treat blood dysentery and lower stomach heat. Cuts, wounds and other dermatological issues like impetigo, eczema and a sore was alleviated using the leaves (Shah *et al.*, 1983; Joshi *et al.*, 1982).
- They had been also used to treat gonorrhoea, fever, leucorrhoea and abnormalities of the urine (Bedi *et al.*, 1978). These stems and leaves were used to treat problems of eyes. Distress and diarrhoea was treated with the leaf powder and stomach ailments are treated with the stem (Shah *et al.*, 1983).
- **Leaf**: The leaves paste had been applied to head for cooling effects, to alleviate from stomach soreness, to treat bleeding shigellosis, to treat prurigo nodularis, pyoderma, dermatitis, cuts, wound healing, urinary problems in females, fluor albus, acute gonorrhoea, nose bleeding, female fertility treatment and menstruation cycle, *etc*., (Logesh *et al.*, 2020).
- **Root:** They had been used as diuretics, tonic, demulcents with regard to the fever, malaria, constipation, arthritis, kidney dysfunction, to treat gastrointestinal pain. It was also used to treat heat and sun strokes (Shah *et al.*, 1983).
- **Blossoms:** They had been used in cooking (Shah *et al.*, 1983).
- **Fruits:** They had been used to make intoxicated liquid refreshments (Joshi *et al.*, 1982). Structure of fruit is depicted in Figure 2.

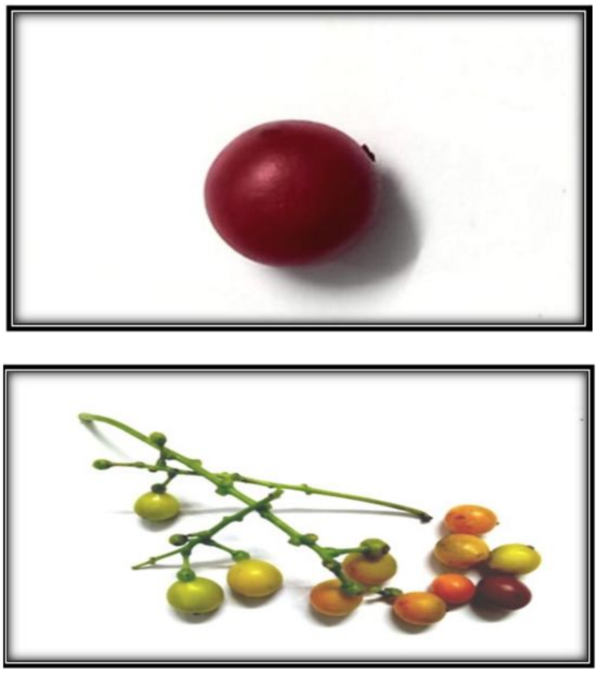

Figure 2: Parts of plant *C. hirsutus* (ripe and unripe fruits).

1.2 Chemical constituents

Although, *C. hirsutus* was extensively used as a traditional medicine and its chemical composition was unknown for the purpose of studying its pharmacological actions (Himadri *et al.*, 1983). Trilobine, isotrilobine, coclaurine and magnoflorine was a few alkaloids detected during preliminary and phytochemical screening, isolation and characterization tests (Panda *et al.*, 2022). There had been more substances like beta-sitosterol, ginnol, and mono-methyl ether of inositol (Merchant *et al.*, 1962). The list of alkaloids depicted in the Table 1. The leaves also include three flavonoids: quercetin, liquiritin and rutin (Patil *et al.*, 2015). A triterpene derivative hirsutol also exists within the plant extract of the whole plant (Vu *et al.*, 1987).

Beta-sitosterol and 28-acetyl botulin was present during the extraction of aerial parts. A lot of things have happened; studies that report the preparatory phytochemical testing of the extracts and demonstrate that the carbohydrates, steroids, alkaloids, glycosides, flavonoids, tannins and saponins were present (Iyer *et al.*, 2011). List of chemical structure is depicted in Figure 3.

Table 1: List of *C. hirsutus* alkaloids that have been discovered

S. No.	Compound name	Plant part/extract	Reference
1.	Jamtinine	Whole plant or ethanolic extract	Meena *et al.*, 2014
2.	Jamtine N-oxide	Whole plant or ethanolic extract	Meena *et al.*, 2014
3.	Haiderine	Whole plant or ethanolic extract	Meena *et al.*, 2014
4.	Hirsutine	Whole plant or ethanolic extract	Ahmad et *al.*, 1993
5.	Cohirsitine	Whole plant or ethanolic extract	Ahmad et *al.*, 1993
6.	Cohirsine	Whole plant or ethanolic extract	Ahmad et *al.*, 1993
7.	Corsutine	Stems and roots or ethanolic extract	Ahmad et *al.*, 1993
8.	Shaheenine	Stems and roots	Rasheed *et al.*, 1991
9.	Magnoflorine	Stems and roots	Rasheed *et al.*, 1991
10.	Trilobine	Stems and roots	Rasheed *et al.*, 1991
11.	Isotrilobine	Stems and roots	Rasheed *et al.*, 1991
12.	Cocsuline-N-2-oxide	Whole plant or ethanol extract	Rasheed *et al.*, 1991

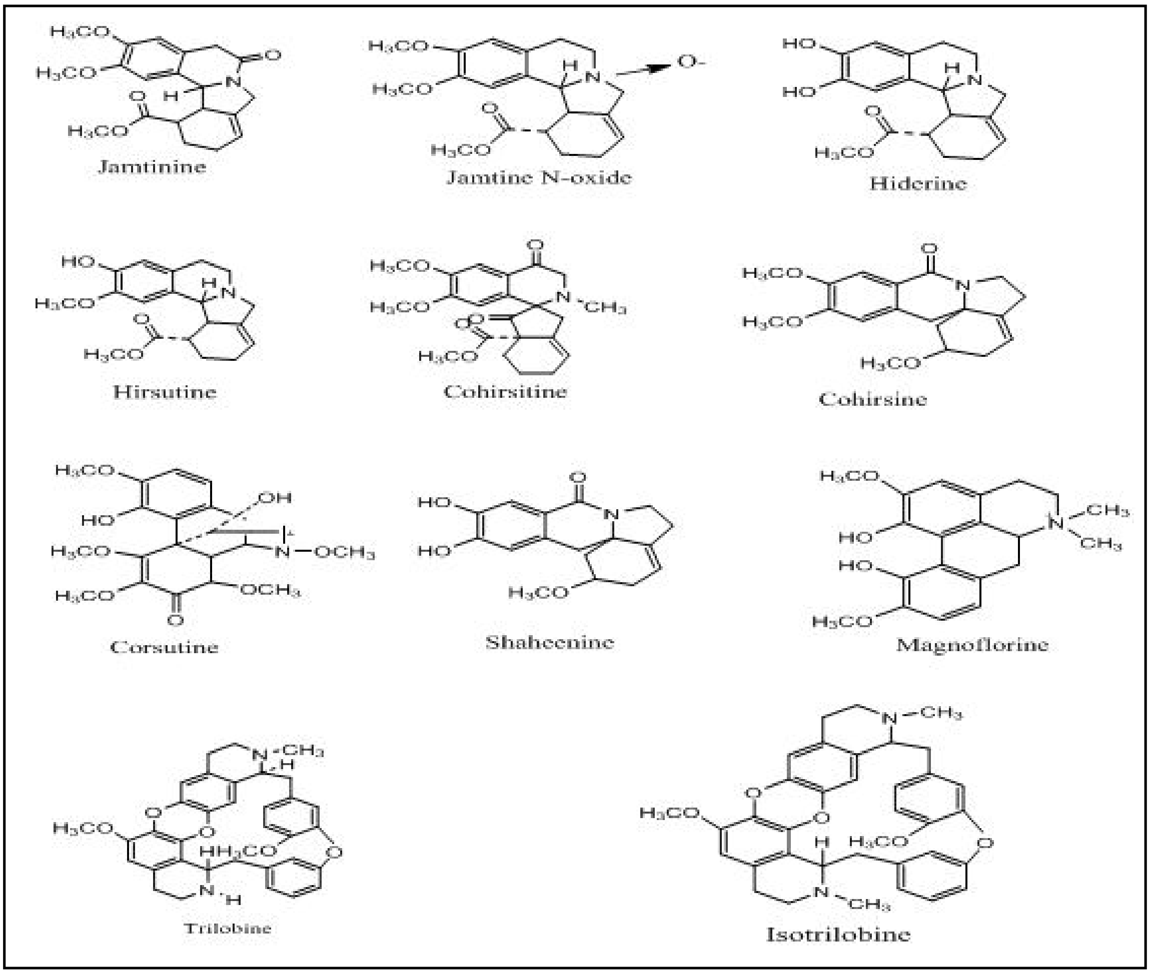

Figure 3: Structure of chemical constituents of plant *C. hirutus*.

2. Materials and Methods

All the above information is taken from some databases including Medline, PubMed, SciFinder, Google Scholar and Scopus connections as well as some secondary sources like books and proceedings. There are some blogs also which has helped in compiling the entire study review together. Some newspapers including Ayurvedic and Herbal information have also played important role here.

3. Pre-clinical studies

The extract made from various *C. hirsutus* plant sections is known to provide incongruity of pharmacological effects.

Table 2: Pharmacological activities and animal used

S. No.	Activities done	Animal/strain/cell culture used	No. of days	Reference
1.	Antimicrobial activity	M. tuberculosis H37Rv strain	28 days	Shabrawy *et al.*, 1984
2.	Antimalarial activity	*Plasmodium falciparum* (chloroquine-sensitive strain)	28 days	Logesh *et al.*, 2020
3.	Insecticidal activity	Plasmodium K1 (chloroquine-resistant strain)	28 days	Brahmam *et al.*, 2018
4.	Immunomodulatory activity	Male/ female wistar rats	14 days	Wahab *et al.*, 2014
5.	Anticancer activity	Breast, melanoma, renal cell line/ Male swiss albino mice	28 days	Rastogi *et al.*, 2008
6.	Antioxidant activity	SD rats	14 days	Thavamani *et al.*, 2014
7.	Antidiabetic activity	Swiss albino mice	28 days	Ramalingam *et al.*, 2012
8.	Hepatoprotective activity	Albino wistar rats	28 days	Badole *et al.*, 2006
9.	Diuretic activity	Wistar rats	28 days	Thakare *et al.*, 2010
10.	Nephroprotective activity	Male wistar rats	15 days	Ganapaty *et al.*, 2002
11.	Cardioprotective activity	Male wistar rats	15 days	Sengottuvelu *et al.*, 2012
12.	Analgesic activity	Male swiss albino mice and rats	7 days	Gadapuram *et al.*, 2013
13.	Anti-inflammatory activity	Male swiss albino mice and rats	7 days	Ranjan *et al.*, 2009

3.1 Antimicrobial activity

When employed at concentrations of 25, 50, 75 and 100 mg/kg b. wt. against isolated bacteria such as *Escherichia coli* (*E. coli*), *Salmonella typhi* (*S. typhi*), *Staphylococcus aureus, etc.* A methanolic, ethanolic and aqueous extract of *C. hirsutus* exhibits strong antibacterial activity. It had been more effective when agar diffusion method was used with ethanolic and petroleum ether extracts. The crude zones of inhibition had been observed when a crude alkaloid fraction was examined at varied doses, suggesting that the extract of ethanol was useful. It also shows that the *C. hirsutus* leaf extract as alternative *M. tuberculosis* H37Rv and other MDR strains had been also effective and suppressed *M. tuberculosis* H37Rv and MDR strains Jal 19187, JAL 1904, JAL-19126, JAL 19188 and JAL 19111 alongwith MIC values of 500, 250, 250, 500 and 500 g/ml (Shabrawy *et al.*, 1984).

3.2 Antimalarial activity

Two species of Plasmodium: K1 (chloroquine-resistant strain) and *Plasmodium falciparum* (chloroquine-sensitive strain) was examined utilizing different extracts of *C. hirsutus* roots and we got to know that both ethanolic and chloroform extracts exhibit strong action against both the Plasmodium strains (Logesh *et al.*, 2020). The success rate of different extract from *C. hirsutus* root in combating malaria was also good.

3.3 Insecticidal activity

Anopheles suboictus larvae and the malaria vector had been employed as study participants for the effectiveness in killing insects by using *C. hirsutus* leaves, which revealed dominant activity with a morality % within 24 h. The success rate of different extract from *C. hirsutus* root in combating malaria in two strains of *P. falciparum, i.e.*, 3D7 (chloroquine-sensitive strain) and K1 (non-chloroquine-sensitive strain) was high. Significant antibacterial activity had been identified in chloroform and methanol extracts (Brahmam *et al.*, 2018).

3.4 Immunomodulatory activity

In mice, the effect of this activity on *C. hirsutus* leaves and *Sesbania grandiflora* flowers had been assessed in the ratios of 1:1, 2:1 and 1:2. A 1:1 blend demonstrates strong immunomodulatory action (Elango *et al.*, 2011). When used against rats that had been immune-suppressed by cyclophosphamide, the aerial component of *C. hirsutus* exhibits dose-dependent actions such as enhanced acceptance, humoral antibody titre (HA), delayed type hypersensitivity reactions and white corpuscle count (Wahab *et al.*, 2014). This works shows that IGM and IGG levels in mice-derived serum was treated with herbal preparation 1, 2 and 3 against sheep red blood cells (SRCB) by applying ELISA method at 0, 4th, 7th and 14th day. After this when the combination of this extract had been given at the dose of 100 and 400 mg/kg b. wt. It helps in increasing the serum antibodies titres after 4th and 7th day. This all over process shows the immunestimulating activity with intonation of B lymphocyte functions. Conclusion: This extract effectively boosted immune system activity and protected it from immune-suppressants (Arunabha *et al.*, 2015).

3.5 Anticancer activity

The rhizome extract of *C. hirsutus* illustrates modest anticancer activity when tested in opposition to breast, melanoma, and renal cell lines (Rastogi *et al.*, 2008). The methanol extract of *C. hirsutus* exhibits considerable cytotoxicity with an IC_{50} value in the MCF-7 HeLa cell line *in vitro*, which is used in another cancer activity against Dalton's lymphoma ascites cells in mice. When dose of extract 200 mg/kg and 400 mg/kg b. wt. are administered, the erythrocyte volume count and tumour cell count are greatly reduced and the haematological and biochemical parameters for serum had been returned to their normal values (Wet *et al.*, 2009).

3.6 Antioxidant activity

C. hirsutus extract exhibits strong (1, 1-diphenyl-2-picrylhydrazyl) DPPH which shows action that scavenges free radicals, ABTS action against free radicals, nitric oxide scavenging activity, decreasing power, suppression of sphingomyelin and metal chelation activity test as ascorbic acid (Thavamani *et al.*, 2014). The pinpointing of the biophysical properties of nanoparticles through a green approach had been rendered feasible by the emergence of cutting-edge technology. In this study, we tackle the prospective antioxidant characteristics of copper nanoparticles (CuNPs) which was prepared in the current investigation by reducing a solution of copper acetate in 3 mM with aqueous *C. hirsutus* leaf extract with copper oxidation nanoparticals was indicated by a colour shift between dark brown and dark green. The greatest intensity of activity that scavenges free radicals was discovered in the H_2O_2 and PMA assays used for assessing the newly generated CuNPs. Additionally, the generated CuNPs illustrated superior antidiabetic exertion in both the assays for modulating glycosidase and amylase (64.4 % 0.11 and 68.4% 0.10, respectively). Lastly, this review shows that *C. hirsutus* had been used in the role of an ecologically sustainable CuNP production and had remarkable *in vitro* antioxidant properties (Ameena *et al.*, 2022).

3.7 Antidiabetic activity

After 28 days of treatment by oral administration of *C. hirsutus* infusions of extract at 250 mg/kg, 500 mg/kg and 1000 mg/kg b. wt. results in a noticeable drop in serum glucose level in mice with an alloxan-induced model. When doing a normal (OGTT), a test for glucose tolerance an extract dose of 1000 mg/kg b. wt. was administered (Ramalingam *et al.*, 2012). *C. hirsutus* leaf extract in water (250, 500 and 1000 mg/kg, respectively, orally, n=6), vehicle (distilled water, 10 ml/kg, orally) or the frequently used medical treatments glyburide (10 mg/kg, orally) had been provided for a total of 28 days to alloxan-induced (70 mg/kg, I.V.) mice having diabetes. The serum glucose level had been determined using the glucose oxidase/peroxidase method subsequent to blood samples was taken via retro-orbital plexus on days 0, 7, 14, 21 and 28. Glyburide (10 mg/kg, P.O.) and mice treated with an aqueous extract of *C. hirsutus* (1000 mg/kg, P.O.) was supplied with glucose (2.5 g/kg, P.O.) during an oral glucose liberality test. At 0, 30, 60, and 120 min following the administration of the medication, glucose was present in the serum monitored. In alloxan-induced diabetic mice at day 28, the aqueous leaf extract of *C. hirsutus* (250, 500, and 1000 mg/kg, P.O.) substantially (p<0.05) suppressed the serum dextrose level. Aqueous extract of *C. hirsutus* boosted oral glucose tolerance outcomes from testing (Badole *et al.*, 2006).

3.8 Hepatoprotective activity

In albino wister rats, oral treatment of *C. hirsutus* methanolic extract at dose of 100, 200 and 400 mg/kg results in lower levels of AST, ALT, ALP, LDH, direct and total bilirubin, and cholesterol (Badole *et al.*, 2006). For this study, 28 days had been endured with biliary duct, commonly occluded. *C. hirsutus* methanol extract had been administered to rats for 28 days and for biochemical investigation and histological investigation, blood and liver biopsy specimens had been taken on day 29. Liver fibrosis was triggered by bile duct ligation, which also prompted reactive oxygen species to be created and oxidative stress to be induced. In order to ascertain the *in vivo* glutathione reductive activity, multiple concentrations of methanolic extract of *C. hirsutus* had been examined. With a substantial rise in circulating marker enzyme levels, liver fibrosis occurs after bile duct ligation. Accelerated hepatic lipid peroxidation, glutathione levels, and the build up of hydroxyl proline brought on by hydrophilic bile acids. Histopathological results further supported the hepatoprotective effects of *C. hirsutus* treatment through dropping the high levels of blood marker enzymes (Thakare *et al.*, 2009).

3.9 Diuretic and nephroprotective activity

When given to normal mice at the dose of 100 and 200 mg/kg, an extract of *C. hirsutus* aerial portions causes an increase in the concentration of the ions Na^+ and K^+ in the urine, confirming an intense diuretic impact (Thakare *et al.*, 2010). The ethanol extract of the leaves of *C. hirsutus* had been used in normal rats to perform another severe and persistent diuretic activity that also raises the concentration of the urine ions Na^+ and K^+. When the ethanolic extract of leaves from *C. hirsutus* had been employed, a rat model that had its kidneys removed exhibits strong nephroprotective action. As a diuretic *C. hirsutus* aerial parts' aqueous extract (100 and 200 mg/kg, orally) had a substantial laxative and diuretic impact in rats. The maximal ethanolic extract dose (400 mg/kg, orally) significantly boosted urine production. Na^+ and K^+ ions as well as Cl ions had been excreted in significantly higher amounts by the control group. An ethanolic extract of *C. hirsutus* leaves (100, 200, and 400 mg/kg orally) or furosemide had no effect on the conc. of Na^+, K^+ and Ca^{++} ions in serum. A combination of furosemide and an ethanolic extract of *C. hirsutus* leaves promoted creatinine excretion in urine but not in agglutinin (Ganapaty *et al*., 2002).

3.10 Cardioprotective activity

When animals had been pretreated with *C. hirsutus* extracts for acute renal hypertension at the dose of 250 and 500 mg/kg orally for 14 days and on 15^{th} day malignant hypertension was instigated and the main arterial blood pressure (MABP) was recorded. High fat diet was given to the animals for the induction of hypercholesterolemia with *C. hirsutus* dose, *i.e.*, 250 and 500 mg/kg for 21 days. As a result the pre-treatment with extract shows decreases MABP, onset of tachycardia and premature ventricular systole. In histology there was no cardiac muscle damage, necrosis and inflammation. A reduction in cholesterol, triglycerides and increase in glucose and high density lipoprotein can be seen hence shows cardio protective effect (Badole *et al.*, 2010).

3.11 Analgesic and anti-inflammatory activity

Pain and inflammation are two most common daily health problems which are generally treated with different traditional remedies. Many nations' traditional medical facilities make use of a variety of natural products. More and more alternative medical practices are becoming more popular to cure an assortment of ailments. Many healing plants offer symptom relief that is comparable to that associated with allopathic therapies to choose from. When the methanol extract of *C. hirsutus* at the dose of 100 and 200 mg/kg is administered orally in opposition to male swiss albino mice, it bewitches peripheral and central analgesic activity. As a result, alternative chemical procedures must be made from substances with minimal adverse consequences of natural origin. Eddie's hot plate model and mouse writhing triggered by acetic acid were used to test the *C. hirsutus* leaf extract in methanol which has analgesic properties. Both *in vitro* and *in vivo* models have been utilized for examination of *C. hirsutus*' anti-inflammatory effects. Rats' *in vivo* paw oedema and granuloma triggered by cotton pellets and carrageenan had been used to investigate the anti-inflammatory effectiveness of human red blood cells membrane stabilization. Both doses of *C. hirsutus* exhibited substantial analgesic effect in Eddy's hot plate analgesic assay (p<0.05 and p<0.01, respectively). The commencement of writhing and its length in the acetic acid-induced writhing model was both delayed and diminished correspondingly, by the methanolic extract of *C. hirsutus*. It demonstrates how the concentration of the extract affects both acute and chronic anti-inflammatory activity (Sengottuvelu *et al.*, 2012).

Comparing the tested group to the control groups, the methanol extract of *C. hirsutus* leaves exhibits most effective healing of wound characteristics (Gadapuram *et al.*, 2013). When oral doses of 100 and 200 mg/kg of the extract had been administered, the aerial component showed a strong laxative effect (Ranjan *et al.*, 2009).

4. Clinical safety studies

Throughout the whole life cycle of drug development, monitoring the patient safety is essential for clinical trials. To establish a methodical approach for safety monitoring, pharmaceutical sponsors must operate pro-actively and constructively with all stakeholders. So, as the regulatory environment has changed plans for risk management, risk evaluation along with risk reduction become more and more necessary (Akhtar *et al.*, 2020). When the sector shifts from inert to strenuous safety surveillance procedures, then there were more of an appetite for creative strategies that use quantitative methods to gather data from all resources, ranging from the findings and presymptomatic cases through the clinical and under probation stages. Probabilistic procedures are crucial tools to help the procedure of safety surveillance become more objective and exacting, notably those predicated on the Bayesian framework (Pilkington *et al.*, 2020). As we know that *C. hirsutus* is responsible for treating various diseases like dengue, tuberculosis, malaria and today's most common problem, *i.e.*, COVID-19. There are number of chemical constituents present in whole plant of *C. hirsutus* and every part of plant is very useful for treatment of many diseases. Here are some futures prospective for this plant is going to play a responsible role in developing new drug medication for the treatment of variety of illnesses related with males and females (Hassanipour *et al.*, 2021).

The bacteria, *Mycobacterium tuberculosis* is the source of most contagious diseases, tuberculosis (TB). The tribal healers of Madhya Pradesh (M.P.), India, have long used a number of medicinal plants to cure a variety of diseases, including TB-related symptoms. The traditional knowledge of plants is factual and does not include rigorous scientific research (Hartoorn *et al.*, 2007). In India to offer a scientific justification for ethnic communities in four regions of M.P.'s traditional use of a few medicinal herbs to cure TB, chest problems and chronic cough became important. The plants ability to prevent the expansion of multidrug-resistant (MDR) Mtb strains was also studied. The cell line for human monocytic leukemia THP-1 macrophages was used to test the active plant extract for common cytotoxicity (Gupta *et al.*, 2017). On the directory of the leading causes of death in India, tuberculosis is among the top three. Drug resistance is one of the key components of factors that can cause patients not react with anti-TB treatment at times and it is vital to look for newer anti-TB medications in view of the rising prevalence of MDR and XDR-TB. For many years now, plants have been showed to be helpful in treating a variety of human ailments (Sabran *et al.*, 2016). According to WHO estimates, 80% of all people's health issues should be treated using herbal medicines as part of their primary care. The current objective is to estimate the antimycobacterial activity of eleven medicinal herbs. The MTT and *Microplate resazurin* assays have been used to test three distinct extracts for their ability as a means of preventing *Mycobacterium smegmatis*. Isoniazid, *C. hirsutus* and *Leptedinia reticulata* have the highest antimycobacterial smegmatis activity percentage among the eleven medicinal plants studied (Hunter *et al.*, 2006). As a result, its findings that in favour of the traditional medical applications of these herbs and can be further investigated for their antimycobacterial activity using more specialized techniques. New antimycobacterial drugs are required since tuberculosis rates are raising globally along with MDR-TB and XDR-TB. This study was evaluated the antimycobacterial abilities of conventionally used medicinal herbs using the MRA as a screening technique (Itah *et al.*, 2005). *L. reticulate* and *C. hirsutus* were shown to have very potent antimycobacterial action in their aqueous extracts. The body of research on plant sources that offered that significant new antimycobacterial chemical is expanding and this study supports long-held beliefs. The *M. smegmatis* strain of mycobacteria was used as the test organism since the experiments were conducted in a bio safety containment level 2 environments. This study examined the antimycobacterial activity of plant extracts against this strain of Mycobacteria. The findings suggest that it would be pertinent to continue researching *L. reticulate* and *C. hirsutus* and current research projects are utilizing the highly virulent *M. tuberculosis* H37Rv strain (Abdullah *et al.*, 2012).

Sinococuline is the main phytobioactive which is responsible for the treatment of most common disease, *i.e.,* dengue as well as COVID-19. Dengue is a virus-based illness spread by mosquitoes that requires the development of a safe and efficient medication. Till now, there is no approved medication and estimated the risk of getting this disease at 50% of the global population. By investigating the traditional Indian medical discipline of Ayurveda, we hoped to create an ethnopharmacological medication to treat dengue. According to previously published study reported this has been led us to discover the creeper *C. hirsutus* as a more effective antidengue plant (Lambeth et al., 2005).

In cell culture, it was discovered that the stem of *C. hirsutus* was superior to its aerial component at suppressing the dissemination of dengue viruses (DENVs). Furthermore, indicating its potential clinical relevance AQCH shielded immune-weakened mice against deadly DENV infection. For the intention of evaluating the calibre and steadiness of extract extraction and tablet formulation, we have discovered five chemical marker components in AQCH. As a result of this investigation the development of a phytopharmaceutical medication derived from *C. hirsutus* for the treatment of dengue has been started (WHO Guidelines, 2009).

There is an indispensable need for an efficient, oral medication for COVID-19, and purified aqueous extract of *C. hirsutus* (AQCH) has demonstrated significant antiviral activity in *in vitro* investigations (Quek *et al.*, 2021). For the first time through a randomized controlled trial, the effectiveness and safety of oral AQCH treatment in hospital patients with intermediate COVID-19 had been evaluated (Beigel *et al.*, 2021). Compared to patients who got standard of care only and those who received AQCH experienced considerably show faster clinical improvement, viral clearance and hospital stay duration (McCreary *et al.*, 2020). These findings highlight the need for more research into AQCH as a COVID-19 treatment that may fasten patient recovery and minimize the load on the healthcare system. The need of taking research results into account holistically within the context of existing knowledge is also highlighted by this study, along with crucial deliberations for the selection of clinical trial endpoints in a relatively new and little acknowledged condition (Spinner *et al.*, 2020).

As we know that the phytochemical standardization of methanolic and ethanolic extract of *C. hirsutus* plant consists of various phytobioactives like phenols, flavonoids, glycosides, triterpenoids, steroids and alkaloids (Jagannadha *et al.*, 1961), further, they are used for pharmacological activities which make them suitable for herbal treatment medication and motivates us to do more *in vivo* and *in vitro* study with parts of plant material. In this same way, anti-inflammatory activity is performed by using human red blood cell methods (Viquaruddin *et al.*, 1992). If methanolic extract has been used then it shows more effective results for inflammation but after comparing leaves to other plant components by *in vivo* (stem) and *in vitro* (callus) studies, it was discovered that leaves, respectively, has been the highest levels of protein, *i.e.*, denaturation (88.8%) and membrane stabilization (65.85%) (Kirtikar *et al.,* 1981). The plant contains different type of secondary alkaloids so if we do a proper isolation for active principles or metabolite it may lead to a development of new field of interest in drug research. Hence a new scope has been developed at a broad spectrum to use *C. hirsutus* as herbal drug treatment for different diseases (Marya *et al.*, 2011).

Table 3: List of different diseases and chemical constituents of extract of *C. hirsutus* used in clinical trial for the therapy

S. No.	Diseases	Chemical constituent/ part of plant used	Part/ parasite involved	Reference
1.	Tuberculosis	Whole plant	*Mycobacterium smegmatis*	Barkan *et al.*, 2009
2.	Dengue	Sinococuline	DENV-infected AG129 mice/ Vero cells	Changal *et al.*, 2016
3.	Malaria	Trilobine	Blood stage of *Plasmodium falciparum*	Zohrameena *et al.*, 2017
4.	COVID-19	Sinococuline	Healthy humans	Dar *et al.*, 2022
5.	Anti-Inflammatory	Whole plant	Human red blood cells	Thiagarajan *et al.*, 2021

4.1 Effect of *C. hirsutus* plant on *Mycobacterium smegmatis*: A tubercular bacilli using mycobacteria growth indicator tube

Since many years ago, plants have been helpful in preventing various human ailments and the objective of this study is also to evaluate the antimycobacterial activity of medicinal plant in comparison to *M. smegmatis*. So, in spite of all control measurements, tuberculosis (TB) has been a leading genesis of death globally and impacts 1/3rd of the world's population. To minimize the long term adverse effects of marketed drug worldwide traditional medical practices have been use to treat a wide range of illnesses with plants preparations (Potterat *et al.*, 2008). 8-9 million new cases of tuberculosis are reported each year, making it a disease that affects people all over the world (Barkan *et al.*, 2009). *M. tuberculosis* which has a 26% global death rate is the cause of tuberculosis. Therefore, in order to find a better cure for these illness additional studies has been conducted which also raised interest in discovering new therapeutic molecules either through an isolation procedure or by extracting them from plants. The most significant drawback of old TB is the high likelihood of the presence of MDR (multi drug resistance) and XDR (extensively drug resistance) strains, which are resistant to many drugs. As to oppose synthetic medications with so many negative consequences herbal plants have few negative effects which are also readily available (Usmani *et al.*, 2016). *C. hirsutus* has been employed as an anti-mycobacterial medication against *M. smegmatis*, a culture that has been freeze-dried for this study has been used. The plant extract was then examined using the MGTI which is a method for detecting the growth of mycobacteria. The MGTI 960 equipment was used to test the antimycobacterial activity. In this process a major supplement for mycobacteria growth was placed in MGTI tubes along with broth medium. Then 100 µl of extract was added and incubated 37°C for 24-72 h. When the time came for inoculation, the bacterial stock solution was preserved in a frozen state and prepared using 7H9 broth media for the distribution of an adequate amount of bacterial cell-containing inoculation volume. The infected media was then put into the MGTI apparatus while it was still heated to 37°C. For positive controls isoniazid or no medication was utilised and for growth control bacterial suspension in MGTI tubes was combined with growth promoters. The positive growth was automatically identified by the equipment but if there was no growth after 72 h, it was deemed negative (Siddiqi *et al.*, 2012).

As a consequence, at a concentration of 500 g/ml *C. hirsutus* aqueous extract demonstrates strong antimycobacterial activity and along with this activity the patient exhibits chemoprotective effects and overall improvement. In conclusion, new drugs that can also be employed as antimycobacterial agents have been needed due to the rise in MDR and XDR TB around the world. *Oscimum sanctum*, *Adhatoda vasica*, *L. reticulata* and *C. hirsutus* are among the medicinal plants exhibiting the greatest concentration of antimycobacterial *smegmatis* activity when juxtaposed with the other eleven studied plants. When compared to isoniazid the two of these four: *L. reticulata* and *C.hirsutus* exhibit substantial inhibition. According to the study's findings it supports the usage of herbs in traditional medicine which also aids in the management and avoidance of tuberculosis. When tested against *M. smegmatis*, the aqueous extract of *C. hirsutus* demonstrated extremely high antimycobacterial activity and a biosafety level (Vaghela *et al*., 2023).

In a further study to acquire particulars on the medicinal plants utilized by the tribes traditional healers, semi-structured discussions and field-walking technique among the indigenous populations of Indian state of M.P.'s Anuppur, Mandla, Umariya, and Dindori districts were used under supervision. The traditional healer of these tribe urged folkloric usage that led to the selection of 35 plant species spread across 22 families (Ahirwar *et al.*, 2015) in which the potential of ethanol extracts of plant to inhibit the growth of six MDR clinical isolates of Mtb and Mtb H37Rv was tested and a conventional resazurin micro titre plate assay (REMA) was used to calculate the minimum inhibitory concentration (MIC) needed to detect the antimycobacterial activity of plants (Bhatia *et al.*, 2014). Using the 3-(4, 5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium (MTT) assay, it was determined that the plant extracts that were reported to be effective against Mtb also had a general cytotoxic effect on human THP-1 macrophages. Furthermore, MIC and cytotoxicity data were also used to compute the selectivity index (SI) of active plant extracts from which we came to know that there are 11 plant species, out of 35 showed antimycobacterial activity with MICs against Mtb H37Rv ranging from 500 to 31.25 g/ml which is specific (Bhatter *et al*., 2016). Six clinical multidrug resistant of Mtb strains had been obtained from sputum samples of pulmonary TB patients were likewise susceptible to the plant extracts' antimycobacterial properties. Active plant extracts' *in vitro* cytotoxicity was also evaluated in human THP-1 macrophages (Copp *et al.*, 2007). Most plant extracts have been shown to have IC_{50} (50% inhibitory concentration) values on THP-1 that were greater than MIC values against Mtb and showed that the THP-1 cells are not negatively impacted at concentrations that were effective against Mtb. Traditional usage of plants namely *Alstonia scholaris* (L.) R. Br., *Glycyrrhiza glabra* L., *Holorrhenaanti dysentrica* (Roth) Wall. Ex A.D.C., *Mallotus philippensis* (Lam.) Müll. Arg., *Eulophia nuda* Lindl., *C. hirsutus* (L.) Diels has been supported by *Pueraria tuberosa* (Willd.) DC., *Cyperus rotundus* L., *Curcuma caesia* Roxb., *Sphaeranthus indicus* L., and *Plumbago zeylanica* L (Eloff *et al.*, 1998). Since our findings indicate that these plants have appropriate antimycobacterial action against Mtb and from this, the current study supports the possible use of plants by tribal healers and traditional applications of several herbs for TB-related symptoms. As a result of consideration, *in vitro* anti-TB activity was discovered. As far as we are aware, the current study is the first to document antimycobacterial activity in plants against Mtb in tribal areas of M.P., India (Gupta *et al.,* 2010).

4.2 Sinococuline: A bioactive compound of *C. hirsutus* with antidengue activity

With approximately 400 million infections each year, dengue virus (DENV) infection has now elevated to a severe public health concern. Aqueous extract of the stem of *C. hirsutus* (AQCH) was recently demonstrated to be safe for use in people and effective against DENV *in vitro* and *in vivo* and we now reveal that sinococuline, which is an active component of AQCH guards AG129 mouse against antibody-mediated subsequent DENV infection (Changal *et al.*, 2016). The public health issue of dengue has recently gotten much worse. Many revised research plans have been made; however, they have not always produced the best final result. The literature study demonstrates that the human dengue virus can be successfully treated *in vivo* and *in vitro* research using an aqueous extract of the stem of *C. hirsutus*. Using the bioactive substance, sinococuline investigation was conducted on the AG129 mouse model. Sinococuline exhibits greater efficacy against DENV-infected AG129 mice when it is delivered IP as opposed to orally. Infusing this bioactive substance intraperitoneally (IP) in infected mice negates intestinal vascular leakage and aids in lessening serum viremia and tissue-viral load. Additionally, when it was given 0.2 mg/kg/day; twice a day; it ceases AG129 mice from becoming DENV-infected. Sinococuline enormously inhibits the proinflammatory cytokines in many mouse organs without causing any negative side effects. By accomplishing a liver function test, it was validated and the investigational dose of sinococuline was shown to be safe in trial according to the histological analysis of the liver. This finding increases researchers' motivation to do additional research in order to meet the demand for antiviral medications for the regimen of DENV infection (Shukla *et al.*, 2021). The high expression levels of pro inflammatory cytokines (TNF and IL-6) in various critical organs were adequately controlled by this dose which also lowered serum viremia and tissue viral load. On the basis of these findings, it could be examined more thoroughly for pre-clinical and clinical innovations.

There is also another study which says that *C. hirsutus* is very effective for the treatment of dengue. This activity was mainly assessed by flow-cytometry based virus inhibition assay and for this we have used the stem extract of particular plant and a solvent system with denatured spirit and hydroalcohol in the ratio of 50:50 in the presence of water (Muller *et al.*, 2017). It was found that stem extract shows more potent activity than its aerial parts. As a consequence of enhancing regulatory legitimacy, the aqueous extract of *C. hirsutus* stem (AQCH) was further advanced for empirical research (WHO, 2017). The release of DENV and its secretary antigen, NS1, was in dose-dependent manner repressed by the AQCH. The key chemical elements of the AQCH extract have been determined: Sinococuline, 20-hydroxyecdysone, makisterone-A, magnoflorine, and coniferyl alcohol (Beesetti *et al.*, 2016). The establishment of a standard of extracts was then accomplished by using these compounds. Importantly, when fed four times daily after infection with a lethal dosage of DENV-2 S221 strain, AQCH completely protected AG129 mice at a dose of 25 mg/kg/dose body weight. AQCH has been revolutionized into tablets to facilitate further pre-clinical and clinical research due to its promise as a strong phytopharmaceutical medication against dengue (Lim *et al.*, 2019).

Findings demonstrates that *C. hirsutus* which is antidengue drug is derived from aptitude is a phytopharmaceutical medication is taken by both intracellularly and *intra vivo*. Additionally, we have identified five chemical components of the drug substance, providing a way to standardize both the drug substance and the drug product. Based on these results, a program has been undertaken to formulate a phytopharmaceutical medications from the *C. hirsutus* plant for the treatment of dengue that is both safe and effective (Dighe *et al.*, 2019).

4.3 Trilobine: A hemisynthetic composite of *C. hirsutus* used for multidrug-resistant *Plasmodium falciparum*

It is necessary to develop new medications that can combat drug-resistant parasites and to eradicate malaria completely. To combat the blood stages of *P. falciparum*, researchers utilized the active component bisbenzylisoquinoline alkaloid found in *C. hirsutus*. This is the hemisynthetic substance which can combat and eradicate the multidrug resistant clinical isolates in the nanomolar range and was discovered among 94 other chemical derivatives (Menard *et al.*, 2017). These 94 hemisynthetic derivatives were used against compound 84 which generally destroys the clinical isolates of multi-drug resistance in nanomolar range. Compound 125, the result of chemical improvement have much better preclinical properties which decreases the onset time of parasite development in mice and inhibit the growth of *P. falciparum*. For this study, the distinct human epigenetic factor have been targeted which hits against asexual blood stage of *P. falciparum*. The blood stage of *P. falciparum* is a stage that results in all clinical symptoms and Trilobine's testing was the target in the population which belongs to the double bridge besbenzylisoquinoline family. The development of disease-causing stage of malaria is lessened by a major chemical change to this component. It influences the stage at which a disease spread as well and against multi-drug resistant clinical segregate, which was originated from Cambodia, this chemical has a prolonged efficacy and exhibits quick effects. Additionally, it features resistance to artemisinin (Zohrameena *et al.*, 2017).

4.4 Aqueous extract of *C. hirsutus* against an antiviral drug for the treatment of COVID-19

For this study, approx 60 healthy humans were taken and divided into 5 groups by arranging them in the ratio of 3:1 to for the treatment. The dose of 100 mg, 200 mg, 400 mg, 600 mg and 800 mg was given to the humans in the form of tablet for 9 days for 3 times daily under a fasting condition of 8 h. At 10th day, single dose was given. After blood testing parameter, a slight increase in Sinococulin peak plasma concentration and total exposure of plasma concentration was obtained at the dose of 600 mg and saturation kinetics at dose 800 mg. Also, there was no change in half-life was seen which confirms the absence of saturation rate of elimination time. Dose accumulation and steady state was obtained in only three days. No interconnection between higher concentrations of sicococuline causing severe adverse effect can be seen during the study. So, this study provides a rational for continuing the use of this extract for the treatment of COVID-19 (Dar *et al.*, 2022). The global dissemination of the new coronavirus SARS-CoV-2 is contributing to the COVID-19 pandemic's rapid spread so; in this circumstance anti-COVID-19 medications are urgently needed. Further, it is anticipated that traditional medicine has found promising new anti-COVID-19 moieties and the goal of this study is to identify phytochemicals from *C. hirsutus* that inhibit the primary SARS-CoV-2 proteases and have anti-COVID-19 action. As a crucial coronavirus enzyme main proteases (Mpro) of SARS-CoV-2 serve as a protuberant target for anti-COVID-19 drug discovery in regulating viral replication and transcription. A recent research has demonstrated that *C. hirsutus* can be used to treat viral diseases like dengue. By using PyRx virtual screen tool and discovery studio visualizer; flavonoids from *C. hirsutus* were identified and used as docking partners against SARS-CoV-2 substantial protein proteases (6LU7, 5R7Y, 5R7Z, 5R80, 5R81, and 5R82). Additionally, simulations of molecular dynamics were run for 100 ns to validate the morphological stability associated with each compound. Then selected *C. hirsutus* phytoconstituents' pharmacokinetic characteristics and drug-likeness prediction were carried out. With a notable increase in binding affinity to SARS-CoV-2 Mpro compared to control, betulin, coclaurine, and quinic acid from *C. hirsutus* were found to be promising. They was identified as potentially intriguing anti-COVID-19 avenues because of stable interactions with the amino acid residues on the majority of the SARS-CoV-2 Mpro's active site. While ethnomedical usage of this herb have been required for its thorough antiviral therapeutic examination and these chemicals could serve as promising leads for the development of target-specific anti-COVID-19 medical treatments (Rajan *et al.*, 2022).

For COVID-19 study procedure, a Phase-2 open-labelled randomized control clinical investigation is conducted with 210 hospital patients and they all was suffering from moderate COVID-19. The aqueous solution of *C. hirsutus* extract has been used for whole study (Wu *et al.*, 2020). The safety and efficacy of drug along with standard care of patient was also evaluated. The patient age ranges from 18-75 were taken in the ration of 1:1 for dosing treatment of 400 mg/kg orally three times a day and a standard special care which was considered as a control group in which no herbal treatment was given. Dose treatment was performed for 10 days only. Clinically, the improvement in patient can be seen after 14 days which was a primary endpoint. And time of clinical improvement, time of clearance, duration of hospitalization can be seen as secondary endpoints (Wang *et al.*, 2020). The majority of patients in both groups had improved clinically by day 14 [difference-0.01(95% CI-0.07 to 0.05); p=0.1]. Comparing the AQCH group to the control group, the median time to clinical improvement was 8 days (IQR 8-11) for the AQCH group it was 11 days (IQR 8-11) [HR 1.27 (95% CI 0.95-1.71); p = 0.032]. The AQCH group have shown significantly shorter hospital stays and virus clearance times (p=0.0002 and p=0.016, respectively) (WHO 2021). No safety problems were found, and AQCH was well tolerated. The time it took for clinical improvement, viral clearance, and hospital stay all considerably decreased with AQCH. Hence, proved that the drug has huge potential to reduce the use of healthcare resources and enhance the availability of hospital beds during a pandemic. So, further research is necessary to determine the therapeutic potential of AQCH in patients with COVID-19 (Thiagarajan *et al.*, 2021).

The data presented here demonstrate that treatment with AQCH improves a number of clinical and viral indicators in hospitalized patients having mild COVID-19, even if no significant difference was observed in the primary endpoint proportion of patients with clinical improvement by day 14 (Padma *et al.*, 2021). In comparison to standard of care alone, oral treatment with AQCH tablets was well tolerated which leads to much earlier normalization of fever, viral clearance, clinical improvement, and a significantly shorter length of hospitalization. So, it is necessary to carry out more research on AQCH's therapeutic potential for COVID-19 patients (Kifle *et al.*, 2021).

5. Discussion

The overwhelming majority for the active next-generation anti-tuberculosis interventions that have been employed as prospective first-line antituberculosis medications are extracts, natural products, and/or semi-synthetic compounds that have been not yet reported on the global pharmaceutical market.

One of the most notable developments in the direction of MGIT is that it is relatively simple to handle, non-radiometric and does not need any sophisticated gear. Our study contrasted MGIT with established techniques for growing acid fast bacteria which defines the most important criteria, *i.e.,* recovery rate, speed and mean time to detection (Tendon *et al.*, 2011; Saikia *et al.*, 2012). It has been extremely dangerous or harmful to diagnose mycobacterial infections quickly. Due to continuous O_2 consumption, monitoring the BACTEC MGIT 960 system became fully automated culture system that enables immediate identification of mycobacteria growing in a liquid medium.

Liquid broth medium has been used in the MGIT assay to promote quicker mycobacterial growth and improved recovery. The Middlebrook 7H9 broth based in the MGIT Tube has been adjusted. On the bottom of the tube there is a silicone-fixed oxygen-quenched fluorochrome in which free oxygen have been used which transformed into carbon dioxide when bacterial growth begins to take place inside the tube. It was when seen under UV light then fluorochrome was no longer been inhibited but attributable to the drop in free oxygen. This caused a spike in fluorescence within the MGIT tube. As the culture tube grew, the algorithm was assessed the percentage of inhibition of bacterial expansion between the sample tube and the culture tube with no sample. Out of eleven investigated plants, the aqueous extracts of *O. sanctum* (71.26), *A. vasica* (74.63), *L. reticulata* (77.91%), and *C. hirsutus* (82.77%) illustrated the strongest antimycobacterial activity. It was discovered that aqueous extracts of *C. hirsutus* and *L. reticulata* at a concentration of 500 g/ml have substantial antimycobacterial implementation (Jethva *et al.*, 2021; Jethva *et al.*, 2020).

Along with their other reported uses as immunomodulators, hepatoprotective, *etc.*, *L. reticulata* and *C. hirsutus* were reported for their antituberculosis use in the literature. This not only aids in preventing tuberculosis but also acts as chemoprotective which ultimately enhances the patient's overall health.

By assessing Sinococuline's protective effectiveness in the secondary dengue AG129 mouse model, the current operates strives to identify its anti-DENV inhibitory property. In severely DENV-infected AG129 mice, sinococuline was substantially more efficacious after being administered intraperitoneally (IP) as opposed to orally. Sinococuline (BID) was reliably infused intraperitoneally to stop the infected mice's intestinal vascular leakage. Additionally, it completely shielded the AG129 mice from secondary DENV infection and successfully suppressed tissue-viral load and serum viremia. Sinococuline, as determined by a liver function test effectively reduces proinflammatory cytokines in numerous tissues without causing any adverse outcomes and the results of the liver pathological research showed that the investigated dose of sinococuline is extremely safe. Overall, these findings support further research and development which will address the critical need for an efficient antiviral medication that can be used to treat DENV infection (Shukla *et al.*, 2023).

Further, we looked at the effects on *P. falciparum* of bisbenzyli soquinoline alkaloids that were obtained from the plant *C. hirsutus*. The synthesis of compound in library of hemisynthetic chemicals dramatically increased the antimalarial activity of trilobine and its natural alkaloids analogues. None of them resistant to multiple drugs clinical isolates from Cambodia which was illustrated cross-resistance to the lead compounds and indicated that this chemical scaffold targets parasite pathways contrasting with those targeted by conventional antimalarial pharmaceuticals. Lead compounds also have a rapid onset of action corresponding to that of artemisinin and chloroquine. The lead molecule also kills the early-ring stage which can withstand high artemisinin concentrations by going dormant and this was a crucial action. When coupled with DHA, the lead compound 84 can revive antimalarial action in isolates that were resistant to artemisinin and highlighting the possibility of this chemical series to be utilized in addition to artemisinin. Natural bisbenzylisoquinoline alkaloids extracted from a variety of plants have already been described for their antimalarial properties and previous re-sensitization for bisbenzylisoquinolines has been described in *P. falciparum* strains resistant to chloroquine as well as in tumor cells resistant to vinblastin (Frappier *et al.*, 1996; Ye *et al.*, 1989).

Though at a higher concentration than in the blood stage compound 125 is likewise concentrating on the liver and transmission (*in vitro* and *in vivo*) stages of *P. falciparum*. As a result, it may be deduced that the protein target(s) were expressed at various times throughout Plasmodium's life cycle. From the parent substance trilobine, we created a chemical probe that we then employed for UV-affinity capture, chemical pull-down, mass spectrometry analysis and deciphering the targeted proteins. Different interactions between proteins and the probe were revealed by target de-convolution of mass spectrometry hits. Through complementary techniques like the production of recombinant proteins, his work lays forth possibilities for subsequent investigations to validate the protein target(s). By making it was easier to increase selectivity in comparison to human homologous protein(s) defining the target that would aid future preclinical drug development processes and result in the delivery of a novel therapeutic candidate (Chakrabarti *et al.*, 1993).

The safety and pharmacokinetics of AQCH tablets in humans were being assessed in this investigation for the first time. All of the normal-weight individuals in each cohort tolerated the test formulation without encountering any substantial clinically relevant adverse events or adverse reactions, which is evidenced by the absence of such events in the laboratory. Since there was a lower number of adverse event documented at greater dosages than at lower levels, the study found no relationship between dose and adverse events (AE). Additional proof from the data supports the lack of a link between systemic sinococuline concentrations and unfavourable outcomes. There have been numerous pharmacokinetic investigations of herbal medications recently. However, unlike allopathic medications it is believed that the pharmacological effects of herbal medicine are caused by the synergistic effects of various components as well as multiple targets and pathways (Bangchang *et al.,* 2021). As a result, pharmacokinetics of herbal medicines is generally more complex than that of synthetic pharmaceuticals. Understanding the relationship between pharmacological and toxicological effects of phytochemicals in the human body and their intensity the time course is made easier with the aid of information on a drug's pharmacokinetic profile. Sinococulin and additionally magnoflorine, makisterone-A, 20-hydroxyecdysone and coniferyl alcohol, four pharmaceutical components of the drug ACQH, have all been reported. In collected plasma, all of these substances were tested for estimation; however, aside from sinococuline measurable amounts of the other substances were negligible and adequate to characterize the pharmacokinetic parameters (Abiramasunadri *et al.,* 2011).

6. Conclusion

As a result, we explored the activity of *C. hirsutus* plant extract against different cases of human diseases caused by virus or parasites like *M. tuberculosis, P. falciparum* and COVID- 19 and found that sinococuline and trilobine bioactive have protective effects against these virus or parasite. Further, for the future prospect as immunomodulatory disorders are common and we are trying to develop new medications from herbal resources *C. hirsutus* provide a wide view to treat different type of diseases may be used. The *C. hirsutus* leaf extract has been shown a dose dependent reaction on immunomodulatory activities will be achievable. It has a number of chemical constituent which are very important and show a significant activity on brain diseases. It motivates the researchers from the future aspect to use herbal resources to develop new medication and minimises the adverse effects and causalities as it is helpful for both males and females. *C. hirsutus* has been used as a very significant herbal remedy for centuries to cure a variety of illnesses like fever, skin conditions, stomach problems, urinary issues, and as a sedative. Jasminitine, hirsutine, cohirsitine and their derivatives were discovered to constitute this drug's main alkaloidal components. Different portions of the plant were also reported to contain flavonoids, terpenoids and other volatile substances.

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Availability of data and materials

All data generated or analyzed during this study are present in this article. All information is collected from the research search engines like PubMed, SciHub, MEDLINE, SciFinder and Google Scholar.

Authors' contribution

AN Compilation of whole data. AS Supervising the whole work. AR Collection of suitable material. TMA Relevant literature search. FA Literature search. SP Editing. SM Formatting. All authors read and approved final manuscript.

Conflict of interest

The authors declare no conflicts of interest relevant to this article.

References

Abdallah, T.M. and Ali, A.A. (2012). Epidemiology of tuberculosis in Eastern Sudan. Asian Pacific Journal of Tropical Biomedicine, **2**(12):999-1001.

Ahirwar, R.K. and Shakya, V.S. (2015). Indigenous ethnomedicinal plants used by baiga tribes in district Mandla, Madhya Pradesh, Central India. Int. J. Sci. Res., **4**:2867-2870.

Ahmad, V. U. and Iqbal, S. (1993). Haiderine, a new isoquinoline alkaloid from *Cocculus hirsutus*. Natural Product Letters, **2**(2):105-109.

Ahmad, V. U.; Mohammad, F. V. and Rasheed, T. (1987). Hirsudiol a triterpenoid from *Cocculus hirsutus*. Phytochemistry, **26**(3):793-794.

Akhtar, S.; Benter, I. F.; Danjuma, M. I.; Doi, S. A., Hasan, S. S. and Habib, A. M. (2020). Pharmacotherapy in COVID-19 patients: A review of ACE2-raising drugs and their clinical safety. Journal of Drug Targeting, **28**(7-8):683-699.

Ameena, S.; Rajesh, N.; Anjum, S. M.; Khadri, H.; Riazunnisa, K. Mohammed, A. and Kari, Z. A. (2022). Antioxidant, antibacterial, and antidiabetic activity of green synthesized copper nanoparticles of *Cocculus hirsutus* (Menispermaceae). Applied Biochemistry and Biotechnology, **194**(10):4424-4438.

Arunabha, M. and Satish, N. (2015). Study the immunomodulatory effects of combined extracts of *Sesbania grandiflora* flowers and *Cocculus hirsutus* leaves on the circulating antibody response. Am. J. Phytomed. Clin. Ther, **3**(3):199-208.

Badole, S. L.; Bodhankar, S. L.; Patel, N. M. and Bhardwaj, S. (2009). Acute and chronic diuretic effect of ethanolic extract of leaves of *Cocculus hirsutus* (L.) Diles in normal rats. Journal of Pharmacy and Pharmacology, **61**(3):387-393. doi:10.1211/jpp.61.03.0015

Badole, S.; Patel, N.; Bodhankar, S.; Jain, B. and Bhardwaj, S. (2006). Antihyperglycemic activity of aqueous extract of leaves of *Cocculus hirsutus* (L.) Diels in alloxan-induced diabetic mice. Indian Journal of Pharmacology, **38**(1):49.

Barkan, D.; Liu, Z.; Sacchettini, J. C. and Glickman, M. S. (2009). Mycolic acid cyclopropanation is essential for viability, drug resistance, and cell wall integrity of *Mycobacterium tuberculosis*. Chemistry and Biology, **16**(5):499-509. doi:10.1016/j.chembiol.2009.04.001

Bedi, S. J. (1978). Ethnobotany of the Ratan Mahal Hills, Gujarat, India. Economic Botany, **32**(3):278-284. doi:10.1007/bf02864701

Beesetti, H.; Khanna, N. and Swaminathan, S. (2016). Investigational drugs in early development for treating dengue infection. Expert Opin-Investig Drugs. **25**(9):1059-1069.

Beigel, J.H.; Tomashek, K.M. and Dodd, L.E. (2020). Remdesivir for the treatment of COVID-19-final report.N Engl J Med. **383**(19):1813-1826. https://doi.org/10.1056/NEJMoa2007764

Bhatia, H.; Sharma, Y.P.; Manhas, R.K. and Kumar, K. (2014). Ethnomedicinal plants used by the villagers of district Udhampur, J and K, India. J Ethnopharmacol. **151**(2):1005-1018.

Bhatter, P.D.; Gupta, P.D. and Birdi, T.J. (2016). Activity of medicinal plant extracts on multiplication of *Mycobacterium tuberculosis* under reduced oxygen conditions using intracellular and axenic assays. Int. J. Microbiol. doi:10.1155/2016/8073079.

Brahmam, P. and Sunita, K. (2018). Phytochemical investigation and *in vitro* antimalarial activity of *Acalypha indica* (L.) and *Cocculus hirsutus* (L.) from Prakasam District, Andhra Pradesh, India. Biomedical and Pharmacology Journal, **11**(4):2123-2134. doi:10.13005/bpj/1592

Chadha Y. (1950). The Wealth of India. CSIR: New Delhi.

Chakrabarti, D.; Schuster, S.M. and Chakrabarti, R. (1993). Cloning and characterization of subunit genes of ribonucleotide reductase, a cell-cycle- regulated enzyme, from *Plasmodium falciparum*. Proc. Natl. Acad. Sci., **90**(24):12020-12024. https://doi.org/10.1073/pnas.90.24.12020.

Changal, K. H. (2016). Differentiating secondary from primary dengue using IgG to IgM ratio in early dengue: An observational hospital based clinico-serological study from North India. BMC Infect Dis., **16**(1):715

Copp, B.R. and Pearce, A.N. (2007). Natural product growth inhibitors of *Mycobacterium tuberculosis*. Nat. Prod. Rep., **24**(2):278-297

Dar, S. K.; Kumar, S.; Maiti, S.; Dhawan, S.; Joglekar, S.; Arora, U. and Khuroo, A. H. (2022). Clinical safety and pharmacokinetic evaluation of aqueous extract of *Cocculus hirsutus*, an antiviral phytopharmacetical drug as a potential for the treatment of dengue and COVID-19. Heliyon, **8**(5):e09416. doi:10.1016/j.heliyon.2022.e09416

De Wet, H.; Fouché, G. and Van Heerden, F. R. (2009). *In vitro* cytotoxicity of crude alkaloidal extracts of South African Menispermaceae against three cancer cell lines. African Journal of Biotechnology, **8**(14):10.

De Wet, H.; Struwig, M. and Van Wyk, B. E. (2015). Taxonomic notes on the genus Cocculus (Menispermaceae) in southern Africa. South African Journal of Botany, **1**(96):99-104.

Dengue: Guidelines for Diagnosis, Treatment, Prevention and Control: New Edition. **(2009)**. WHO Guidelines Approved by the Guidelines Review Committee. Geneva.

Dighe, S.N.; Ekwudu, O.; Dua, K.; Chellappan, D.K.; Katavic, P.L. and Collet, T.A. (2019). Recent update on antidengue drug discovery. Eur. J. Med. Chem., **176**:431-455.

Elango, G.; Rahuman, A. A.; Kamaraj, C.; Bagavan, A. and Zahir, A. A. (2011). Efficacy of medicinal plant extracts against malarial vector, *Anopheles subpictus* Grassi. Parasitology Research, **108**(6):1437-1445. doi:10.1007/s00436-010-2192-4

Eloff, J.N., (1998). Which extractant should be used for the screening and isolation of antimicrobial components from plants? J. Ethnopharmacol, **60**(1):1-8.

Frappier, F.; Jossang, A.; Soudon, J.; Calvo, F.; Rasoanaivo, P.; Ratsimamanga-Urverg, S.; Saez, J.; Schrevel, J. and Grellier, P. (1996). Bisbenzylisoquinolines as modulators of chloroquine resistance in *Plasmodium falciparum* and multidrug resistance in tumor cells. Antimicrob. Agents Chemother, **40**:1476-1481. https://doi.org/10.1128/AAC.40:6:1476.

Gadapuram, T. K.; Murthy, J. S. N.; Rajannagari, R. R.; Kandati, V.; Choda, P. K. and Shukla, R. (2013). Nephroprotective activity of *Cocculus hirsutus* leaf extract in 5/6 nephrectomized rat model. Journal of Basic and Clinical Physiology and Pharmacology, **24**(4):299-306. doi:10.1515/jbcpp-2013-0007

Ganapaty, S.; Dash, G. K.; Subburaju, T. and Suresh, P. (2002). Diuretic, laxative and toxicity studies of *Cocculus hirsutus* aerial parts. Fitoterapia, **73**(1):28-31. doi:10.1016/s0367-326x(01)00345-8

Gunjegaonkar, S. M.; Khakal, V. R.; Joshi, A. A.; Nargund, S. L.; Shinde, S. D. and Khan, N. S. (2022). Cardioprotective effect of *Cocculus hirsutus* in experimental hypertension in rats. Journal of Ayurveda and Integrative Medicine, **13**(4):100652. doi:10.1016/j.jaim.2022.100652

Gupta, R.; Vairale, M.G.; Deshmukh, R.R.; Chaudhary, P.R. and Wate, S.R., (2010). Ethnomedicinal uses of some plants used by gond tribe of Bhandara district, Maharashtra. Indian J. Tradit. Knowl, **9**(4):713-717.

Gupta, V.K.; Kumar, M.M.; Bisht, D. and Kaushik, A., (2017). Plants in our combating strategies against *Mycobacterium tuberculosis*: Progress made and obstacles met. Pharm. Biol., **55**(1):1536-1544

Hartkoorn, R.C.; Chandler, B.; Owen, A.; Ward, S.A.; Bertel S.S.; Back, D.J. and Khoo, S.H., (2007). Differential drug susceptibility of intracellular and extracellular tuberculosis, and the impact of P-glycoprotein. Tuberculosis, **87**(3):248-255

Hassanipour, S.; Arab-Zozani, M.; Amani, B.; Heidarzad, F.; Fathalipour, M. and Martinez-de-Hoyo, R. (2021). The efficacy and safety of Favipiravir in treatment of COVID-19: A systematic review and meta-analysis of clinical trials. Scientific Reports, **11**(1):11022.

Hemadri, K. and Rao, S. S. (1983). Leucorrhoea and menorrhagia: Tribal medicine. Ancient Science of Life, **3**(1):40-41.

Hunter, R.L.; Olsen, M.R.; Jagannath, C. and Actor, J.K. (2006). Multiple roles of cord factor in the pathogenesis of primary, secondary and cavitary tuberculosis, including a revised description of the pathology of secondary disease. Annals of Clinical and Laboratory Science, **36**(4):371-386

Itah, A.Y. and Udofia, S.M. (2005). Epidemiology and endemicity of pulmonary tuberculosis (PTB) in Southeastern Nigeria. Southeast Asian Journal of Tropical Medicine and Public Health, **36**(2):317-323.

Iyer, S. V.; Shankul, K. and Parikh, P. M. (2011). Isolation of phytoconstituents from the aerial parts of *Cocculus hirsutus* Linn. J. Pharm. Res., **4**:1946-1947.

Jagannadha, R.K.V. and Ramachandra, R.L. (1961). Chemical examination of *Cocculus hirsutus* (Linn) Diels. J Sci Ind Res., **20**:125-126.

Jethva, K.D.; Bhatt, D.R. and Zaveri, M.N. (2021). Antimycobacterial screening of selected medicinal plants using mtb and the microplate resazurin assay. Int. J. Pharm. Sci. and Res., **12**(3):1537-1545.

Jethva, K.D.; Bhatt, D.R. and Zaveri, M.N. (2020). Antimycobacterial screening of selected medicinal plants against *Mycobacterium tuberculosis* H37Rv using agar dilution method and the microplate resazurin assay. Int. J. Mycobacteriol., **9**:150-155e

Joshi, P. (1982). An ethnobotanical study of Bhils-A preliminary survey. J. Econ. Tax. Bot., **3**(1):257-268.

Kifle, Z.D.; Ayele, A.G. and Enyew, E.F. (2021). Drug repurposingapproach, potential drugs, and novel drug targets for COVID-19 treatment. J. Environ. Public Health, **21**(6):631721. https://doi.org/10.1155/2021/6631721

Kirtikar, K.R. and Basu, B.D. (1981). Indian Medicinal Plants. Lalit Mohan Basu, Allahabad, **2**(3):80-90.

Lambeth, C.R.; White, L.J.; Johnston, R.E. and De Silva, A.M. (2005). Flow cytometry based assay for titrating dengue virus. J. Clin. Microbiol., **43**(7):32-72.

Lim, S.P. (2019). Dengue drug discovery: Progress, challenges and outlook. Antiviral Res., **163**:156-78.

Marya, H.B. and Bothara, B.S. (2011). Ethnopharmacological properties of *Cocculus hirsutus* (L.) Diels: A review. Int. J. Pharm. Sci. Review, Res., **7**(1):108-112

McCreary, E.K. and Angus, D.C. (2021). Efficacy of remdesivir in COVID-19. JAMA., **324**(11):1041-2. https://doi.org/10.1001/jama.2020.16337

Meena, M. K.; Singh, N. and Patni, V. (2014). Determination of bioactive components of the leaves of *Cocculus hirsutus* (L.) Diels using GC-MS analysis. Int. J. Pharm. Pharm. Sci., **6**:327-329.

Menard, D. and Dondorp, A. (2017). Antimalarial drug resistance: A threat to malaria elimination. Cold Spring Harbor perspectives in medicine, **7**(7):1121-1133.

Merchant, J. R.; Naik, R. M. and Hirwe, S. N. (1962). Chemical investigation of *Cocculus hirsutus* (L.) Diels. J. India Chem. Soc., **39**:411-416.

Muller, D.A.; Depelsenaire, A.C. and Young, P.R. (2017). Clinical and laboratory diagnosis of dengue virus infection. J. Infect. Dis., **215**:S89-S95

Na-Bangchang, K.; Kulma, I.; Plengsuriyakarn, T.; Tharavanij, T.; Kotawng, K.; Chemung, A. and Karbwang, J. (2021). Phase I clinical trial to evaluate the safety and pharmacokinetics of capsule formulation of the standardized extract of *Atractylodes lancea*. Journal of Traditional and Complementary Medicine, **11**(4):343-355.

Abiramasundari, P.; Priya, V. and Jeyanthi, G.P. (2011). Evaluation of the antibacterial activity of *Cocculus hirsutus*, Hygeia J. Drugs Med., **3**:26-31

Padma, T.V. (2021). Indian Government should heed its scientists on COVID. Nature, **9**:593(7857). https://doi.org/10.1038/d41586-021-01140-6

Panda, B. R.; Mohanta, S. R.; Mishra, U. S.; Kar, S.; Panda, B. K. and Chakraborty, P. (2007). Antibacterial activity of the leaves of *Cocculus hirsutus*. Indian Drugs - Bombay, **44**(2):108.

Panda, N.; Mishra, B.; Kar, N. R.; Panigrahi, S. P.; Dash, R. N. and Gangopadhyay, A. (2022). Phytochemical constituent and its pharmacological application of various types of chemical compounds present in *Cocculus hirsutus* (L.) Diels. Journal of Positive School Psychology, **6**(8):992-1000.

Patil, V.; Angadi, S.; Devdhe, S. and Wakte, P. (2015). Recent progress in simultaneous estimation of rutin, quercetin and liquiritin in *Cocculus hirsutus* by HPTLC. Research Journal of Pharmacognosy (RJP), **2**(4):49-55.

Pilkington, V.; Pepperrell, T. and Hill, A. (2020). A review of the safety of favipiravir: A potential treatment in the COVID-19 pandemic. Journal of Virus Eradication, **6**(2):45-51.

Potterat, O. and Hamburger, M. (2008). Drug discovery and development with plant-derived compounds. Natural Compounds as Drugs, **1**:45-118.

Quek, E.; Tahir, H.; Kumar, P.; Hastings, R. and Jha, R. (2021). Treatment of COVID-19: A review of current and prospective pharmacotherapies. Br. J. Hosp. Med. (Lond), **82**(3):1-9. https://doi.org/10.12968/hmed.2021.0112

Rajan, M.; Prabhakaran, S.; Prusty, J.S.; Chauhan, N.; Gupta, P. and Kumar, A. (2022). Phytochemicals of *Cocculus hirsutus* deciphered SARS-CoV-2 inhibition by targeting main proteases in molecular docking, simulation, and pharmacological analyses. Journal of Biomolecular Structure and Dynamics, pp:1-5.

Ramalingam, R.; Suganyadevi, P. and Aravinthan, K. M. (2012). Quantitative phytochemical analysis and their antioxidant activity of *Cocculus hirsutus* (l.) Diel's fruit. International Journal of phytomedicine, **4**(4): 447.

Ranjan, P. B.; Mohanta, S. R.; Sii, S. and Das, G. K. (2009). Preliminary phytochemical analysis and wound healing activity from the leaves of *Cocculus hirsutus* Diels. International Journal of Pharmaceutical Sciences and Nanotechnology (IJPSN), **2**(3):675-678. doi:10.37285/ijpsn.2009.2.3.13

Rasheed, T.; Khan, M. N. I.; Zhadi, S. S. A. and Durrani, S. (1991). Hirsutine: A new alkaloid from *Cocculus hirsutus*. Journal of Natural Products, **54**(2):582-584. doi:10.1021/np50074a037

Rastogi, B.; Tiwari, U.; Dubey, A.; Bawara, B.; Chauhan, N. S. and Saraf, D. K. (2008). Immunostimulant activity of *Cocculus hirsutus* on immunosuppressed rat. Pharmacologyonline, **3**:38-57.

Rufaida; Mahmood, T.; Kedwai, I.; Ahsan, F.; Shamim, A.; Shariq, M. and Parveen, S. (2021). A dossier on COVID-19 chronicle. Journal of Basic and Clinical Physiology and Pharmacology, **33**(1):45-54.

Sabran. S.F.; Mohamed, M.; Bakar, A. and Fadzelly, M. (2016). Ethnomedical knowledge of plants used for the treatment of tuberculosis in Johor, Malaysia. Evidence-Based Complementary and Alternative Medicine, pp:1-12.

Saikia, D.; Parveen, S.; Gupta, V.K. and Luqman, S. (2012). Anti-tuberculosis activity of Indian grass (*Vetiveria zizanioides* L. Nash). Complementary Therapies in Medicine. **20**(6):434-436.

Sengottuvelu, S.; Rajesh, K.; Sherief, S. H.; Duraisami, R.; Vasudevan, M.; Nandhakumar, J. and Sivakumar, T. (2012). Evaluation of analgesic and anti-inflammatory activity of methanolic extract of *Cocculus hirsutus* leaves. J. Res. Educ. Indian Med., **18**(3-4):175-182.

Shah, G. L.; Yadav, S. S. and Nath, B. (1983). Medicinal plants from Dahanu forest division in Maharashtra state. Journal of Economic and Taxonomic Botany, pp:1-19.

Shrestha, K. K.; Bhattarai, S. and Bhandari, P. (2018). Handbook of Flowering Plants of Nepal (Vol. 1 Gymnosperms and Angiosperms: Cycadaceae -Betulaceae). Scientific Publishers, pp:970.

Shukla, R.; Ahuja, R.; Beesetti, H.; Garg, A.; Aggarwal, C.; Chaturvedi, S. and Khanna, N. (2023). Sinococuline, a bioactive compound of *Cocculus hirsutus* has potent antidengue activity. Scientific Reports, **13**(1):1026.

Shukla, R.; Rajpoot, R. K.; Poddar, A.; Ahuja, R.; Beesetti, H.; Shanmugam, R. K. and Khanna, N. (2021). *Cocculus hirsutus*-derived phytopharmaceutical drug has potent antidengue activity. Frontiers in Microbiology, **12**:746110. doi:10.3389/fmicb.2021.746110

Slatkin, D. J.; El-Shabrawy, A. O.; Schiff Jr, P. L.; Gupta, B. D.; Ray, A. B. and Tripathi, V. J. (1984). Cocsuline-N-2-oxide, a new alkaloid from Cocculus hirsutus DC. Heterocycles, **22**(5):993-995.

Spinner, C.D.; Gottlieb, R.L. and Criner, G.J. (2020). Effect of remdesivir vs standard care on clinical status at 11days in patients with moderate COVID-19: a randomized clinical trial. JAMA, **324**(11):1048–57.https://doi.org/10.1001/jama.2020.16349

Tandon. R.; Ponnan, P.; Aggarwal, N. and Pathak R. (2011). Characterization of 7-amino-4-methylcoumarin as an effective antitubercular agent: structure-activity relationships. Journal of Antimicrobial Chemotherapy, **66**(11):2543-2555.

Thakare, S. P.; Jain, H. N.; Patil, S. D. and Upadhyay, U. M. (2009). Hepatoprotective effect of *Cocculus hirsutus* on bile duct ligation-induced liver fibrosis in albino wistar rats. Bangladesh Journal of Pharmacology, **4**(2): 126-130.

Thakare, S. P.; Deore, H. V.; Patil, S. D.; Yende, S. R.; Upadhyay, U. M. and Thakare, M. S. P. (2010). Evaluation of hepatoprotective effect of *Cocculus hirsutus* (L) diels on ethanol induced hepatic damage in albino wistar rats. Reviews, pp:401-413.

Thavamani, B. S.; Mathew, M. and Palaniswamy, D. S. (2014). Anticancer activity of *Cocculus hirsutus* against Dalton's lymphoma ascites (DLA) cells in mice. Pharmaceutical Biology, **52**(7):867-872. doi:10.3109/13880209.2013.871642

Thiagarajan K. (2021). Why is India having a covid-19surge? BMJ, **373**:1124. https://doi.org/10.1136/bmj.n1124.

Usmani, A.; Mujahid, M. D.; Khushtar, M.; Siddiqui, H. H. and Rahman, M. A. (2016). Hepatoprotective effect of *Anacyclus pyrethrum* Linn. against antitubercular drug-induced hepatotoxicity in SD rats. Journal of Complementary and Integrative Medicine, **13**(3):295-300.

Vaghela, K.; Bhatt, D. and Zaveri, M. (2021). Effect of ethanomedicinal plants on *Mycobacterium smegmatis* Tubercular bacilli using mycobacteria growth indicator tube assay. Plants, pp:13-21.

Viquaruddin A and Iqbal S (1992). Cohirsitine, A new isoquinoline alkaloid from *Cocculus hirsutus*. Fitoterapiam, **63**:308-310

Wahab, S.; Hussain, A.; Farooqui, A. H. A.; Ahmad, M. P.; Hussain, M. S.; Rizvi, A.; and Ansari, N. H. (2014). *In vivo* antioxidant and immunomodulatory activity of *Bombax ceiba* bark-Focusing on its invigorating effects. Am. J. Adv. Drug. Deliv., **2**(1):1-13.

Wang, Y.; Zhang, D. and Du, G. (2020). Remdesivir in adults with severe COVID-19: A randomised, double-blind, placebo-controlled, multicentre trial. Lancet, **395**(10236):1569-78. https://doi.org/10.1016/S0140-6736(20)31022-9

World Health O. (2017). Dengue vaccine: WHO position paper, July 2016 - recommendations. Vaccine. **35**(9):1200-1201

World Health Organization. (2021). WHO Coronavirus (COVID-19) Dashboard. https://covid19.who.int/table.

Wu, Z. and McGoogan, J.M. (2020). Characteristics of and important lessons from the coronavirus disease2019 (COVID-19) outbreak in China: Summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA, **323**(13):1239-1242. https://doi.org/10.1001/jama.2020.2648

Ye, Z.G.; Van Dyke, K. and Castranova, V. (1989). The potentiating action of tetrandrine in combination with chloroquine or qinghaosu against chloroquine-sensitive and resistant falciparum malaria. Biochem. Biophys. Res. Commun., **165**:758-765. https://doi.org/10.1016/s0006-291x(89)

Zohrameena, S.; Mujahid, M.; Bagga, P.; Khalid, M.; Noorul, H.; Nesar, A. and Saba, P. (2017). Medicinal uses and pharmacological activity of *Tamarindus indica*. World Journal of Pharmaceutical Sciences, pp:121-133.

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