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СИНДРОМ ШНИЦЛЕРА – НЕДОСТАТОЧНО ДИАГНОСТИРУЕМОЕ АУТОВОСПАЛИТЕЛЬНОЕ ЗАБОЛЕВАНИЕ: ПЕРСПЕКТИВЫ В НАСТОЯЩЕМ И БУДУЩЕМ

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Резюме. Синдром Шницлера – редкое, но обычно малодиагностируемое аутовоспалительное заболевание, которое характеризуется моноклональной IgM-гаммапатией, персистирующей крапивницей, перемежающейся лихорадкой, болями в костях и артралгией или артритом. Впервые о нем сообщила д-р Лилиан Шницлер в 1972 г. Однако этот синдром остается проблемным в плане диагностики, и постановка этого диагноза обычно занимает более 5 лет. Он проявляется в виде крапивницы, артрита, органомегалии, лихорадки, лимфаденопатии, высоких значений СОЭ, лейкоцитоза и болей в костях. В его патогенезе центральными являются иммунологические нарушения и активация инфламмасом. Его типичная диагностика происходит при клинико-анамнестическом обследовании и выявлении важных признаков, в частности моноклональной гаммапатии и острой или рецидивирующей сыпи типа крапивницы. В лечении применяют синтетические препараты, в том числе анакинру, канакинумаб, рилонасепт и антагонисты IL-6 с разной степенью эффективности. Недавние исследования показали также, что растительные препараты, такие как *Terminalia chebula*, *Emblica offcinalis*, *Schinus terebinthifolia*, *Ferula*, базилик и *Wedelia,* могут потенциально контролировать симптомы заболевания и влиять на воспалительные пути. Перспективы медицинского применения этих растений, согласно данным, полученным *in silico*, предполагают дальнейшие исследования их клинического использования. При новых методах лечения, обещающих лучшие клинические исходы, болезнь Шницлера в целом является существенной терапевтической проблемой.

Ключевые слова: синдром Шницлера, аутовоспалительное заболевание, веделолактон, IgM, IgG, моноклональное антитело, NLRP3-мозаицизм, NLRP3-инфламмасома

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SCHNITZLER'S SYNDROME, AN UNDERDIAGNOSED AUTOINFLAMMATORY DISEASE: CURRENT AND FUTURE PERSPECTIVE

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Abstract. Schnitzler's syndrome is a rare but usually underdiagnosed autoinflammatory disease, characterized by monoclonal IgM gammopathy, persistent urticaria, intermittent fever, bone pain, and arthralgia or arthritis. Although first reported by Dr. Liliane Schnitzler in 1972, the syndrome continues to pose challenges in diagnosis, and it usually takes more than five years before it is properly identified. Disorders show up in a form of urticaria, arthritis, organomegaly, fever, lymphadenopathy, high ESR, leukocytosis, and bone pain. Central to its pathogenesis are immunologic perturbations and activation of the inflammasome. It is typically diagnosed through clinical exam with history and important feature identification such as monoclonal gammopathy and acute or relapsing urticarial rash. Therapeutically synthetic agents include anakinra, canakinumab, rilonacept, and anti-IL-6 have been used with variable success. Recent research also demonstrated how natural treatments such as *Terminalia chebula*, *Emblica offcinalis*, *Schinus terebinthifolia*, tulsi, asafoetida, and *Wedelia* plants have the potential for controlling the symptoms and changing inflammatory paths. Promising medicinal possibilities for these plants, according to *in silico* investigations, point to further research into their clinical uses. With new therapy paths that promise better patient outcomes, Schnitzler's illness is overall a therapeutic challenge.

Keywords: Schnitzler's syndrome, auto-inflammatory disease, Wedelolactone, IgM, IgG, monoclonal antibody, NLRP3 mosaicism, NLRP3 inflammasome

Introduction

Recurrent fever rash, bone and joint pain, swollen lymph nodes, exhaustion, a monoclonal IgM component, leukocytosis, and systemic inflammatory response are indicative of the uncommon and underdiagnosed adult disease known as Schnitzler's syndrome. Schnitzlerэы syndrome is an unusual but treatable disease distinguished by persistent urticaria, intermittent fever, bone pain, arthralgia or arthritis, and monoclonal IgM gammopathy. Dr. Liliane Schnitzler, a French dermatologist, characterised it first in 1972, and more than 40 patients have subsequently reported it. In most cases, the disease goes undiagnosed for more than 5 years. This syndrome's wide range of clinical symptoms involves dermatologists, internists, rheumatologists, and haematologists. This has become an important concern because major morbidities have been experienced by patients with systemic inflammation when left untreated. It has been considered an adult-onset auto-inflammatory disease [19, 41, 58, 68].

Symptoms

A number of symptoms are associated with Schnitzler's syndrome including urticaria, arthritis, organomegaly, fever, lymph nodes, enlarged liver or spleen, high ESR, leukocytosis, bone pain, and anomalies in haemopoiesis [40] and more symptoms involves like increased platelet count due to thrombocytosis, neutrophil leukocytosis, monoclonal gammopathy, increasing ESR or CRP, decreasing complement levels, anaemia associated with a chronic disease, and increased IgM levels [6].

Aetiology

Aside from its unknown exact origin, immune system dysregulation is the main cause of Schnitzler's syndrome, an auto-inflammatory disease characterized by high inflammatory markers, joint pain, fever, and recurring urticarial rashes. The most salient feature is the monoclonal gammopathy of IgM or IgG [28, 52].

Pathophysiology

Immune system dysregulation, inappropriate inflammasome activation, and overproduction of proinflammatory cytokines are the hallmarks of Schnitzler's syndrome, an autoinflammatory disorder [34]. The cause of chronic inflammation and increased inflammasome activation could be due to NLRP3 inflammasome mutations induced by somatic NLRP3 mosaicism (Figure 1) [13, 25].

Diagnosis

Clinical diagnosis and diagnosis by patient history are essential for the diagnosis of Schnitzler's

syndrome. The most critical diagnostic findings include monoclonal gammopathy, usually IgMκ, sometimes IgG, and urticarial rash resistant to antihistamines, and persistent or recurrent. The presence of a monoclonal gammopathy, specifically IgMκ, in conjunction with clinical signs such as urticaria and systemic inflammation, is usually sufficient to make the diagnosis of SchS. Examples of SchS patients who do not exhibit gammopathy but respond favourably to IL-1 treatment suggest that the diagnostic criteria may be overly stringent. Even in the absence of gammopathy, laboratory abnormalities such as high ESR, CRP, and particular skin biopsy results can help in the diagnosis of Schnitzler-like disorders [22, 67, 68, 77].

– Erythrocyte Sedimentation Rate (ESR): A slightly elevated level, a sign of inflammation.

– C-Reactive Protein (CRP): Another indicator of inflammation that is elevated.

– Interleukin-6 (IL-6) and IL-2 Levels: Elevated, suggesting the presence of an inflammatory condition.

– Monoclonal IgM Component Serum protein electrophoresis revealed it, which is a crucial characteristic of Schnitzler's syndrome.

– Normal TNFα and IL-8 Levels: These offer more context but do not rule out Schnitzler's syndrome.

– Normal Creatinine, Complete Blood Count (CBC), and Serum Calcium: These typical outcomes aid in ruling out further diseases.

– No Bence-Jones Proteinuria: This aids in ruling out multiple myeloma.

– Normal Skeletal X-rays, Bone Marrow Aspirates, and Histology: These results aid in excluding further hematologic and skeletal diseases.

– Normal Cerebral and Thoracic Scans, Abdominal Sonography: The normal imaging studies aid in excluding further systemic illnesses.

Types of treatment

Different treatment modalities exist for the comprehensive management of Schnitzler's syndrome, which altogether can be categorized as synthetic and natural ways, each of which gives a unique role in symptomatic relief and treatment of the mechanisms underlying the autoinflammatory disorder.

Synthetic treatment for Schnitzler's syndrome

Before these treatments, the syndrome could not be effectively treated with more than thirty drugs. Although substantial dosages of corticosteroids were necessary for some patients, antihistamine treatment had no impact. Low serum amyloid is the goal of IL-1 blocking treatments like rilonacept, canakinumab, and anakinra [45].

1. Anakinra

Recombinant IL-1ra anakinra binds to the IL-1 receptor very firmly but does not cause signal transduction. It was initially licenced to treat rheumatoid arthritis, and then it was also approved to treat deficiency of IL-1 receptor antagonists and neonatal-onset multisystem inflammatory disease. Martinez-Toboada et al. documented the first instance of anakinra being successfully treated to Schnitzler's syndrome, with a high effectiveness rate of up to 94% [45]. Nonetheless, certain studies propose utilising the anakinra therapy response as a standard for Schnitzler's syndrome. Anakinra is highly effective in treating Schnitzler's syndrome; 83% of patients experienced complete remission and 17% experienced partial remission, according to observational research. Another group of 21 Schnitzler syndrome patients experienced both full and partial remission, and all of them saw long-term benefits with anakinra treatment [20, 36, 42, 50, 60, 64].

2. Canakinumab

Human monoclonal antibody canakinumab is used to treat a variety of conditions, such as systemic juvenile idiopathic arthritis, FMF, hyper-immunoglobulin D syndrome/mevalonate kinase deficiency, MWS, TRAPS, older familial cold auto-inflammatory syndrome, and CAPS in both adults and children. 34 Schnitzler syndrome patients received treatment in all, and 58.6% of them reported having a full recovery. Over nine months, eight patients had a persistent therapeutic benefit. In a randomised, placebo-controlled research, canakinumab was used to treat five out of seven individuals, while no

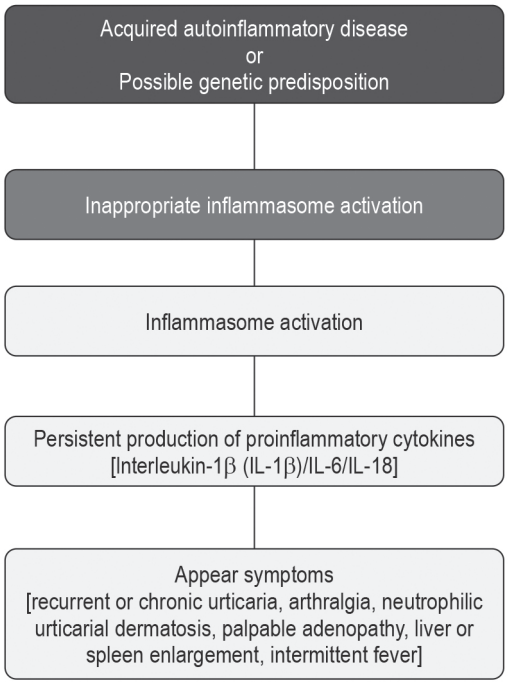


Figure 1. Schnitzler's syndrome's pathophysiology

response was seen in the 13 patients who received a placebo. All patients demonstrated a durable response to canakinumab over 4 years, with normalising levels of SAA and C-reactive protein. This demonstrates canakinumab's ongoing treatment efficacy for Schnitzler's syndrome [8, 23, 37, 39].

3. Rilonacept

A recombinant fusion protein called rilonacept targets IL-1 receptors and inhibits them from attaching to the IL-1 receptor found on cell membranes. The European Medicines Agency and the US Food and Drug Administration have authorised it for the treatment of CAPS. Eight individuals in a clinical trial who satisfied Lipsker diagnostic criteria were given a loading dosage of 320 mg and then a 160 mg subcutaneous injection per week. GPA and the Schnitzler activity score were used to gauge the clinical results. Three patients had a partial response, and fifty per cent of patients had complete or almost complete remission at the one-year follow-up. Within 24 hours of the initial dosage, the therapeutic effects started to take effect [32, 36, 38, 41, 50].

4. Anti-IL-6 treatment

Treatment outcomes for Schnitzler's syndrome with tocilizumab, an anti-IL-6 drug, have been inconsistent. When tocilizumab was infused, some patients went into complete remission, while others did not react well. In one clinical research, tocilizumab helped some patients at first, but with time, those benefits were lost. It was also mentioned that tocilizumab medication may not have been as beneficial for certain individuals in Japan. In general, individuals with Schnitzler's syndrome who do not respond to IL-1 blockers may be candidates for tocilizumab monotherapy; however, for improved results, it may also be administered in combination with other immunosuppressants. To learn more about the long-term effectiveness and possible recurrence rates of tocilizumab treatment for Schnitzler's syndrome, more investigation and observation are required [11, 12, 17, 69, 79].

5. Rituximab

Rituximab is a monoclonal antibody that is used to treat ANCA-associated vasculitis, rheumatoid arthritis, and B-cell lymphoma. Although no clinical trials have been done, it might be useful in treating Schnitzler's syndrome. When used in conjunction with other medications, rituximab has demonstrated a good response in certain cases but not in others [3, 5, 16, 24, 48, 55, 72, 78].

6. Anti-TNF

Etanercept, adalimumab, and drome are examples of TNF inhibitors. Only one article demonstrates that adalimumab There was no improvement or escalation of symptoms seen [21, 71].

7. Anti-IL-17 therapies

Schnitzler's syndrome patients have lesional skin that contains IL-17A, and neutrophils are the source of this substance. Being a potent neutrophil chemoattractant, IL-17A causes cutaneous lesions and dermal infiltration. Those who do not respond to IL-1 blockers may benefit from anti-IL-17 therapy [7, 21, 50, 60, 69, 71, 76].

Natural treatment for schnitzler syndrome

Schnitzler's syndrome can be effectively treated with medicinal plants, the formulation of rare auto-inflammatory conditions. Table 1 presents traditional plants used for preventing and treating this condition.

1. Terminalia chebula

The medicinal herb *Terminalia chebula*, which has a wide range of therapeutic uses, is traditionally used to treat urticaria, arthritis, fever, organomegaly, and lymphadenopathy [1]. Furthermore, studies have demonstrated the potential of *Terminalia chebula* extract to ameliorate doxorubicin-induced haematological problems by enhancing haemoglobin content, total white blood cell count, and antioxidant status [26]. Furthermore, research on *Terminalia chebula* has demonstrated its antioxidant, anti-inflammatory, and anticancer properties, indicating that it is a suitable option for additional study in cancer treatment [30, 44].

The wide array of the pharmacological actions of *Terminalia chebula* might, therefore, be helpful in some ways while treating the various manifestations of Schnitzler's syndrome, although the contexts cited do not relate to its efficacy in any specific symptom pertinent in the case, such as elevated ESR, leukocytosis, and abnormalities of hemopoiesis. Chelagic acid isolated from *Terminalia chebula* reduces inflammation through the modification of proinflammatory cytokines. Studies have shown that chebulagic acid inhibited the increase in IL-1β and TNFα production induced by LPS. It has also been proven to inhibit the production of pro-inflammatory cytokines like TNFα, IL-6, and IL-1β through repression of the p38 MAPK pathway. It was also established that chebulinic acid exhibited anti-inflammatory activity by the inhibition of protein denaturation, which may justify further study of the anti-inflammatory properties of the plant. Together, these results point to the importance of chebulagic acid in modulating proinflammatory cytokines by enhancing osteoblast functions, decreasing oxidative stress, and inhibiting NF-κB signalling, as demonstrated in studies on LPS-induced bone loss. This provides a promising therapeutic approach for inflammatory conditions such as Schnitzler syndrome [31, 81].

In silico studies of Terminalia chebula

– The docking studies of *Terminalia chebula* unravel a great therapeutic potential due to its good binding affinity with the amino acids as shown in Figure 2. The phyto-constituents of T. chebula are

TABLE 1. LIST OF MEDICINAL PLANTS USED FOR THE PREVENTION AND TREATMENT OF SCHNITZLER'S SYNDROME

S. No.	Plant	Family	Chemical composition used in Schnitzler's syndrome	Common name	Part of the plant used
1	*Terminalia chebula*	Combretaceae	Chebulagic acid	Black myrobalan	Fruit
2	*Emblica officinalis*	Phyllanthaceae	Ellagic acid	Amla	Fruit, seed, leaves, root, bark and flowers
3	*Schinus terebinthifolia*	Anacardiaceae	Gallic acid	Brazilian peppertree	Bark, leaves
4	Tulsi plant	Lamiaceae	Ursolic acid	Holy basil	Leaves, stem, flower, root, seeds
5	Asafoetida	Umbelliferae	*Ferula assa-foetida*	Devil's dung, hing	Root, leaves, and stem
6	*Wedelia* plant	Asteraceae	Wedelolactone	Yellow dots	Leaves

one day going to be developed into potent medication options.

– The molecular dynamics simulations show the stability of these interactions and prove their potential for medication development. Experiments in vitro confirmed the antioxidant activities of T. chebula, showing that it can block oxidative reactions, a critical function.

– Even though the docking experiments are very promising for the species, further in vivo studies will be necessary to establish its therapeutic efficacy and safety profile for clinical application.

2. Emblica officinalis

Ellagic acid, a substance with strong anti-inflammatory qualities, is found in *Emblica officinalis*, commonly referred to as Indian gooseberry or Amla. Because ellagic acid has been shown to target proinflammatory cytokines, it may be able to treat inflammatory disorders such as Schnitzler's syndrome. This has been the subject of much research. According to studies, ellagic acid's anti-inflammatory properties are achieved through modulating inflammatory signals and cytokines, including TNFα, IL-1β, and IL-6. AKT1, VEGFA, TNF, and MAPK3 are some of the important targets of ellagic acid that have been linked to inflammation, according to research employing a network pharmacology approach. It has been demonstrated that ellagic acid administration decreases pro-inflammatory cytokine levels, such as TNFα and IL-1β, while raising anti-inflammatory cytokines, such as IL-10 and IFNγ, hence lowering arthritis-associated pathology in animal modelsThese findings support the fact that ellagic acid contained in *Emblica officinalis* could modulate the effects of Schnitzler's syndrome, by its action on inflammation responses through various different molecular pathways and focusing particularly on proinflammatory cytokines [4, 9, 31, 49].

In silico studies of Emblica officinalis

– *Emblica officinalis* has a good binding affinity with amino acids, and its complex phytochemical profile makes it a potential option for medicinal application as seen in Figure 2. This action will not only make it highly bioactive but also place it in an excellent position for use in modern medicine.

– Its ability to complexation with amino acids means that the absorption and, therefore, the efficacy of these medicaments would be higher and therefore better outcomes for patients.

– While most of the medicinal potential for Amla has already been well documented, further studies are needed to understand the mechanism of its interaction with amino acids and to standardize its extracts for clinical use.

3. Schinus terebinthifolia

Traditional medicine used *Schinus terebinthifolia*, sometimes referred to as capoeira, to treat a range of ailments, including inflammatory diseases like arthritis [59]. The herb exhibits anti-inflammatory and restorative qualities, but there isn't much research on how it affects certain conditions like Schnitzler's syndrome. Monoterpenes, sesquiterpenes, and phenols are among the bioactive components found in *Schinus terebinthifolia*, and they may be beneficial for illnesses involving organomegaly, fever, lymph nodes, and hemopoiesis dysregulation [75]. With the low cytotoxicity and antibacterial activity, it becomes equally important to understand the therapeutic benefits and limitations of the essential oil from *Schinus terebinthifolia* against a wide range of health conditions [14]. Gallic acid is one such polyphenolic component of *Schinus terebinthifolia* and many other natural sources, and there are various ways it can affect the levels of proinflammatory cytokines. TNFα, IL-1β, and IL-6 are the proinflammatory cytokines which gallic acid effectively reduces by

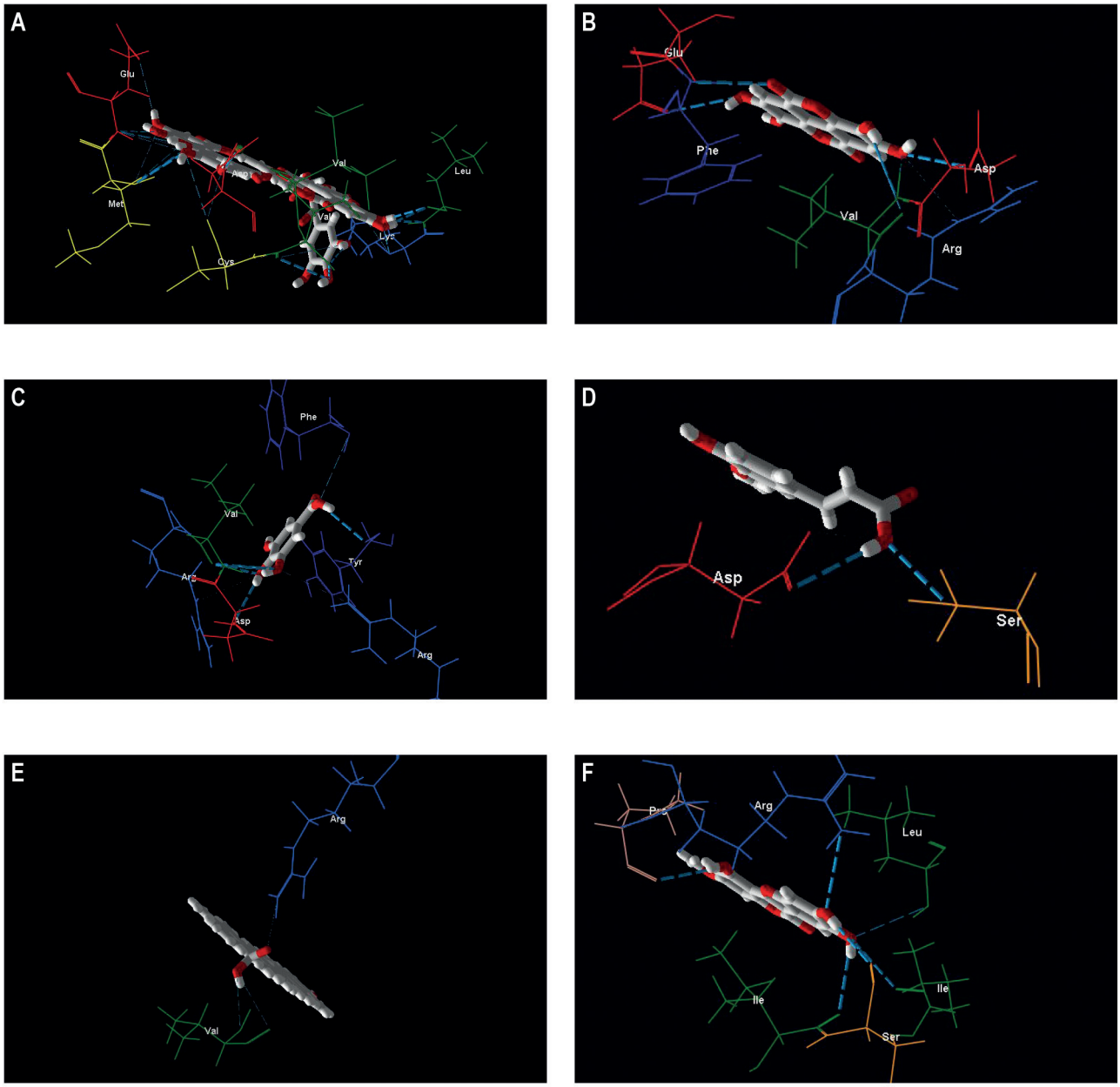


Figure 2. Binding pose of chief phytoconstituents in the active site

Note. A, chebulagic acid; B, ellagic acid; C, gallic acid; D, ferulic acid; E, ursolic acid; F, wedelolactone.

downregulating its gene and inhibiting the signaling pathways such as NF-κB [51, 74, 80]. It also exerts anti-inflammation by inhibition of myometrial contractions, reducing the expression of labour-associated proteins in fetal tissues, and regulating the production of proinflammatory mediators and cytokines [46]. Further, gallic acid has shown anti-inflammatory and antioxidant action in respect of polycystic ovarian syndrome by reducing the amount of oxidative stress, inflammatory cytokines, lipid peroxidation, and DNA oxidative damage in ovarian tissue [62]. All things considered, gallic acid is a viable option for the treatment of inflammatory illnesses and disorders due to its capacity to regulate proinflammatory cytokines.

In silico studies of Schinus terebinthifolia

In silico studies on *Schinus terebinthifolia* (Figure 2), focusing on gallic acid, have remarked on its remarkable binding affinity with multiple amino acids, showing much potential as a therapeutic agent. *In silico* studies use the molecular docking and computing study interactions of gallic acid against various target proteins. Such studies suggest that gallic acid and other phytochemicals could be encouraging candidates for drug development in thrombin activity and skin disorders. Such findings are in need of further

validation in vitro and in vivo to confirm the findings and find out the fullest therapeutic potentiality of *Schinus terebinthifolia*.

4. Tulsi plant

Tulsi, scientifically known as *Ocimum sanctum*, is a highly valued medicinal herb with diverse therapeutic uses [61]. Traditionally, this plant has been used in Ayurveda and other forms of traditional medicine for the management of various diseases and disorders, including but not limited to organomegaly, urticaria, arthritis, fever, disorders of lymph nodes, and abnormalities of haemopoiesis. Some of the major medicinal values of tulsi are attributed to its anti-inflammatory, antioxidant, and immunomodulatory properties. These uses are facilitated by the phytochemical elements found in different portions of the plant, including as eugenol, vallinin, gallic acid, and linoleic acid [57, 61, 83]. These qualities make tulsi a useful natural therapy for treating a range of health issues, possibly including those related to Schnitzler's syndrome [70], while particular clinical research on this illness has not yet been done. The plant tulsi (*Ocimum sanctum*) and other plants contain ursolic acid, a pentacyclic triterpenoid that has been shown to have powerful anti-inflammatory effects. Important inflammatory cytokines like IL-6, IL-8, TNFα, IL-1β, and IL-18 can be inhibited by ursolic acid, according to studies. Many disorders, such as psoriasis, cerebral haemorrhage, and chronic prostatitis, have been discovered to have their inflammatory responses attenuated by ursolic acid through numerous routes, including the NF-κB/NLRP3/GSDMD pathway [29, 43, 54, 65].

In silico studies of Tulsi

– The *in silico* studies regarding Tulsi (*Ocimum sanctum*) were conducted with molecular docking and analysis of bioactive components that indeed pointed out the plant's great binding affinity with several amino acids as portrayed in Figure 2. In our findings, draws attention to the significant role Tulsi plays in the treatment of a number of medical disorders within the purview of modern medicine, and now it is becoming critical in drug discovery and development.

– It has been reported that tulsi has a wide range of pharmacological action, including anti-bacterial, anti-inflammatory, and anti-cancer activities.

5. Asafoetida

Asafoetida, which is derived from the *Ferula assa-foetida* plant, has been used traditionally to treat several diseases that are linked to Schnitzler's syndrome, including urticaria, arthritis, fever, organomegaly, lymph nodes, enlarged liver or spleen, elevated ESR, leukocytosis, bone soreness, and irregularities in hemopoiesis [2, 10, 33, 47, 66]. The plant is good for a variety of diseases due to its therapeutic characteristics, which are attributed to its bioactive components, which include coumarins, volatile oils, and ferulic acid. Antifungal, anti-inflammatory, antiviral, and antioxidant activities make asafoetida useful in food preparation owing to its immense pharmacological importance. Galvanic acid is among the identified compounds in asafoetida, which indicates the anti-cancerous activities of the plant, further indicating various medicinal applications of the plant. Anti-inflammatory activity has been reported with *Ferula assa-foetida* – an asafoetida supply plant – by modulation of proinflammatory cytokines especially in its ethanolic extract fraction. It is due to studies that have shown the ethanolic extract of *Ferula assa-foetida* oleo-gum-resin significantly reduced intracellular ROS formation and suppressed the expression of ICAM-1 and VCAM-1; there is less adhesion of PBMCs [27]. The anti-inflammatory action of *Ferula assa-foetida* gum-resin extract has been attributed to its rich content of antioxidant flavonoids and phenolic components which inhibit lipoxygenase activity [35]. Additionally, it has been documented that member of the genus *Ferula*, especially *Ferula assa-foetida*, influence different cytokines and reduce inflammatory mediators, demonstrating their potential as therapeutic agents against inflammatory diseases [73].

In silico studies of Asafoetida

The interactions of ferulic acid with amino acids at the active site of proteins, especially *Ferula assa-foetida*, offer a pharmacological potential for it. *In silico* studies revealed that ferulic acid binds well with the key amino acids to enhance bio-activity and point toward the therapeutic application as shown in Figure 2.

However, while these computational findings turn out to be promising, further experimental validation needs to be done to confirm the very mechanism of binding and understand the full therapeutic potential of Asafoetida.

6. Wedelia plant

Many studies have been conducted on the potential medical benefits of *Wedelia* plants, especially *Wedelia chinensis*, for treating a variety of conditions, including fever, coughing, phlegm, and liver damage [15, 53, 57]. *Wedelia chinensis* has been reported to contain chemicals with important biological activities, such as steroids and diterpenes, which have been proven to have anti-acetylcholinesterase, antioxidant, and cytotoxic properties [56]. Some of these substances may be medically useful. Antifungal activities of *Wedelia* species were also investigated and some interesting compounds were isolated that showed promising potentials in further studies and development into medication [18]. Induction of polyploidy in *Wedelia chinensis* was also conducted to increase the quality and medicinal value of the plant, therefore demonstrating the usefulness and potential therapeutic uses of the plant [53]. Accordingly, the

great variety of bioactive compounds and medicinal properties within the diverse species of *Wedelia* would show a very wide range of potential health benefits that could be investigated against a number of conditions, including those related to Schnitzler's syndrome-even though these contexts do not specifically mention the connection between Schnitzler's syndrome and *Wedelia* plants. Wedelolactone is obtained from a *Wedelia* plant and has anti-inflammatory properties due to the ability to modulate pro-inflammatory cytokines through various pathways. In collagen-induced arthritis (CIA) mice, studies reveal that wedelolactone reduces the release of pro-inflammatory cytokines like IL-1β, IL-6, TNFα, and IL-18 [82]. Furthermore, Wedelolactone has been observed to potentiate PKA signalling to extensively decrease NLRP3 inflammasome activation, pyroptosis, and IL-1β secretion in macrophages. Furthermore, in murine macrophages driven to an inflammatory response by zymosan, wedelolactone inhibits the release of TNFα, IL-6, and IL12p40. Additionally, Wedelolactone inhibits oxidative stress and inflammation by targeting soluble epoxide hydrolase (sEH) to increase EET levels and regulate Nrf2 and NF-κB pathways in LPS-stimulated acute lung damage models [82]. Together, our results highlight the diverse anti-inflammatory characteristics of wedelolactone in regulating proinflammatory cytokines via several mechanisms.

In silico studies of Wedelia plant

Wedelolactone, the bioactive compound extracted from *Wedelia* plant, showed prominent binding interactions with amino acids as shown in Figure 2, proving the potential of the compound as a drug. The phytoconstituents present in this plant are amino acids, flavonoids, and phenolic compounds, enhancing its nutritional and therapeutic value. *Wedelia trilobata* has potent anti-inflammatory activities due to its interaction with amino acids. The potential of Wedelolactone for the treatment of diseases is varied, thus justifying the possibility of its positive interaction with amino acids. Further research is essential to clearly understand the mechanism behind these interactions and their therapeutic applications.

Conclusion

Characterized by chronic urticaria, recurring fever, bone pain, arthralgia or arthritis and monoclonal IgM gammopathy, Schnitzler's syndrome is a rare but treatable disorder in adults. It is a rare auto-inflammatory disease that often remains unrecognized for more than five years. Symptoms include urticaria, arthritis, fever, lymph nodes, swollen liver, or spleen, raised ESR, leukocytosis, bone pain, and abnormalities in haemopoiesis. Immune system dysregulation is the major cause of this autoinflammatory condition. Synthetic treatment for Schnitzler's syndrome includes anakinra, canakinumab, rilonacept, and a combination of these drugs. Anakinra is highly effective in treating Schnitzler's syndrome, with 83% of patients experiencing complete remission and 17% experiencing partial remission. Canakinumab is used to treat various conditions, including systemic juvenile idiopathic arthritis, FMF, hyperimmunoglobulin D syndrome/mevalonate kinase deficiency, MWS, TRAPS, older familial cold auto-inflammatory syndrome, and CAPS in both adults and children. Medicinal plants have shown potential benefits in managing some aspects of the syndrome by modifying proinflammatory cytokines, inhibiting lipopolysaccharide-induced elevation of IL-1β and TNFα, and enhancing osteoblast functions. *Terminalia chebula*, *Emblica officinalis*, *Schinus terebinthifolia*, Tulsi plant, Asafoetida, *Wedelia* plants, and Wedelolactone have shown potential in treating Schnitzler's syndrome. *In silico* studies on *Terminalia chebula* and Tulsi have highlighted its great binding affinity with amino acids, highlighting its significant role in modern medicine and drug discovery and development. Asafoetida has been traditionally used to treat various diseases linked to Schnitzler's syndrome, and Wedelolactone has anti-inflammatory properties due to its ability to modulate proinflammatory cytokines through various routes. Further research is needed to understand the mechanism behind these interactions and their therapeutic applications.

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