https://doi.org/ 10.33472/AFJBS.6.9.2024.1311-1330

African Journal of Biological Sciences

Journal homepage: http://www.afjbs.com

Research Paper Open Access

Pazopanib: Effective monotherapy for precise cancer treatment, targeting specific mutations and tumors

Rashmi Pathak[1*], Virender Kaur[2], Surabhi Sharma[1], Maulshree Bhandari[1], Riya Mishra[1], Archita Saxena[1], Arpita Upreti[2], Himanshu Sharma[4]

1. Department of Pharmacy, Invertis University, Bareilly, (UP)-243123, India
2. College of Pharmacy, Graphic Era Hill University, Bhimtal campus, (Uttarakhand)-263136, India
3. Amrapali University, Siksha Nagar, Lamachaur, Haldwani, Nainital, (Uttarakhand)-263139, India
4. Teerthanker Mahaveer College of Pharmacy, Teerthanker Mahaveer University, Moradabad (UP)-244001, India

***Corresponding Author**

Rashmi Pathak

Department of Pharmacy, Invertis University, Bareilly (UP)-243123, India

Email id: rashmipathak963@gmail.com

Article History

Volume 6,Issue 9, 2024

Received: 26-03-2024

Accepted : 28-04-2024

doi: 10.33472/AFJBS.6.9.2024.1311-1330

Abstract

Cancer is a wide range of illnesses characterized by the expansion of abnormal cells with the ability to invade and damage healthy bodily tissue. Cancer is treated with a variety of chemotherapy or chemo medicines, Busulfan, and the alkylating agent. Soft tissue sarcoma is the uncommon kind that occurs in the tissues that encircle, link, and support other body structures. This includes the lining of your joints, blood vessels, muscles, and blood vessels. The soft tissue sarcoma family includes 50 subtypes. Pazopanib is used to treat specific cancers (soft tissue sarcoma). Tyrosine kinase inhibitors are a class of medications that includes pazopanib. Pazopanib treatment for soft tissue sarcoma and its mode of action are the current areas of emphasis.

Keywords: Pazopanib, personalized medicine, pharmacokinetics, soft tissue sarcoma, angiogenesis

1. Introduction to neoplasm

In the twenty-first century, cancer is predicted to rank as the largest cause of death, anticipated 29.5 million incident cases and 16.4 million fatalities by 2040, according to the (IARC) the International Agency for Research on Cancer, World Health Organization (2020). Globally, cancer claims more lives than TB, malaria, diabetes, and HIV/AIDS combined [1]. The major obstacles in oncology include cancer's molecular heterogeneity, expensive, ineffective medications, and rising resistance to chemotherapy and radiation treatments [2]. To identify effective cancer treatment plans, more research is therefore essential [3]. More and more studies have been conducted since the 1990s to support the notion that cancer stem cells exist [4]. The main cause of the difficulty in treating and preventing tumors from returning is the involvement of cancer stem cells in the stability and maintenance of tumor heterogeneity [5]. According to one theory, heterogeneity comes from several cell types, such as those cells that have stem cell-like properties [6]. There is less evidence of its advent whether they are actively produced or mutated into stem cells, there is another theory that suggests that a variety of tumors result from clonal evolution, and that mutant tumor cells can survive and grow [7]. A dominant mutant cell can support tumor growth and resembles stem cells [8]. The two viewpoints are not exclusive of one another but rather have internal relationships [9]. Radiotherapy (RT) will be used to treat at least 60% of cancer patients [10]. Due to the rarity and variety treatment for STSs (soft tissue sarcomas) is difficult [11]. Surgery along with supplemental RT is the primary mode of therapy [12]. DNA-interacting ionized intracellular compounds and reactive oxygen species are two ways that RT causes DNA alterations in cancer cells and healthy cells [13]. Numerous downstream cell death processes, including for instance, apoptosis, necrosis, and irreversible cell cycle arrest, are triggered by Single-strand breaks (SSB) and double-strand breaks (DSB), two types of DNA damage [14]. The tumor's innate radioresistance, the tumor microenvironment's radiosensitivity, and the surrounding normal tissues, however, limit the effectiveness of RT in the treatment of cancer [15].

2. Types of cancer

2.1 Glioma

Up to 80% of brain cancers are tumors of gliomas, which are the most prevalent type of adult brain cancer [16]. Despite being the most common primary brain tumor, glioblastoma (GBM) is a kind of glioma that accounts for 57.3% of these tumors and has the worst prognosis: WHO grade IV [17]. There are two distinct categories for gliomas [18]. First, roughly 90% of all GBMs are IDH wild-type tumors, or de novo primary GBMs, which are typically found in older patients (R62 years). Second, secondary GBM, which only accounts for 10% of cases and more frequently affects patients between the ages of 40 and 50, is the IDH mutant kind. Low-grade astrocytomas give rise to IDH mutant tumors [19].

2.2 Liver

Two common digestive gland malignancies are liver cancer and pancreatic cancer [20]. The sole remaining option for pancreatic cancer patients and liver cancer to receive a radical cure is surgical resection [21]. A late or distant metastasis prevents the majority of patients from having surgery. Most patients will experience local or distant metastases even after major surgery, which will ultimately result in death [22].

2.3 Breast cancer

Breast cancer is one of the most prevalent malignant tumors that puts women's health in danger worldwide [23]. Breast cancer treatment still faces several difficulties, Despite the advancement of diagnostic and treatment methods such as surgery, endocrine therapy, immunotherapy, and adjuvant chemoradiotherapy, certain problems still exist, such as simple metastasis and a high recurrence rate [24-27]. Therefore, it is crucial to monitor the activity of cancer cells while they are present and stop tumor metastasis through early detection and therapy. For the detection of various malignancies, several techniques are available, including Reverse transcription-polymerase chain reaction (RT-PCR), computed tomography (CT), magnetic resonance imaging (MRI), and immunohistochemistry analyses [28]. Although these techniques can accurately identify cancer in vitro, they require complex preprocessing when used at the biological level, which makes real-time in-vivo detection challenging [29]. Optical imaging is a noninvasive method for identifying cancer in situ fluorescence in real-time, as opposed to conventional detection procedures [30]. Currently, fluorescent probes that respond to enzymic tumor biomarkers with fluorescent "off-on" signals can be used to visualize cancer cells [31-33]. In fluorescence-guided surgery, these probes have developed into a potent biological tool [34-37].

2.4 Gastrointestinal cancer

According to GLOBOCAN 2018, there will be 9.6 million cancer-related fatalities and 18.1 fresh instances of cancer worldwide in 2018 [38]. 2018 was predicted to see over 1,000,000 new cases of stomach cancer, 783,000 fatalities, and new cases of colorectal cancer totaling 1.8 million, resulting in an anticipated 881,000 fatalities. In all, gastrointestinal (GI) tract malignancies were responsible for nearly 15% of new cases and 17% of cancer-related fatalities. The next-most common cancers are colorectal and gastric cancer common cancers in China, respectively, and the third and fifth most common causes of cancer mortality [39]. Compared to the US and the UK, with digestive tract malignancies accounting for 36.4% of all cancer-related fatalities, China has a lower cancer incidence than the US, but a 30%–40% higher cancer fatality rate [40]. The most efficient GI cancer therapies are surgical resection, radiation, and medication therapy. Due to late diagnosis, GI cancer has an extremely poor prognosis., despite advances in medication research. Immunotherapy, targeted therapy, and chemotherapy are the primary types of pharmacological therapy used for GI cancer. the status of things right now suggests that to increase the number of drug clinical studies for GI cancer, we urgently need to promote more of them [41].

2.5 Soft tissue sarcoma

About 1%–2% of all malignancies are "soft tissue sarcomas" (STS), a rare cancer originating derived from mesenchymal connective tissue. Annually, 12750 new cases are identified in the USA, and STS causes 5270 fatalities [42]. In the 28 EU member states, 4.71 per 100,000 people were affected by STS individuals in Europe. There were reportedly 25851 new cases [43]. Traditional histology and molecular genetics are combined in the diagnosis and are based on the 2013 WHO classification of soft tissue tumors [44]. It can be difficult to diagnose mesenchymal tumors solely based on morphology and immunohistochemical staining, even though some sarcomas exhibit distinctive such as spindle cells, epithelioid or epithelial-like cells, myxoid tumors, round cells, and pleomorphic morphology [45]. Furthermore, a traditional histologic diagnosis frequently lacks a clear direction for anticancer therapy [46]. Cytogenetic PCR, targeted sequencing, and molecular genetic analysis, such as Fluorescence

in situ hybridization, karyotyping, and reverse transcription, are increasingly often used biomarkers for diagnosis and treatment decision-making in the sarcoma diagnostic work-up [47].

3. Types of soft tissue sarcoma

The two main neoplasm groups that make up the heterogeneous sarcoma tumor category are:

3.1 Bone sarcomas and soft tissue sarcomas

Soft tissue sarcomas are mesodermal in origin and typically start in the body's muscle, fat, fibrous tissue, blood vessels, or other supporting tissue. These sarcomas make up about 1% of adult cancers and 7% of pediatric cancers. The most common varieties among the cancers arising from fibrous tissue are fibrosarcoma and malignant fibrous histiocytoma., Leiomyosarcoma from smooth muscle, liposarcoma from fatty tissue, muscle-derived rhabdomyosarcoma and angiosarcoma, Blood and lymph vessel-related lymphangiosarcomas and Kaposi sarcoma, perivascular tissue-derived hemangiopericytoma, 0.2% of all new cancer diagnoses are bone sarcomas, which peak older adults (secondary sarcomas) and adolescents (initial sarcomas) linked to Irradiated bones and Paget disease). Ewing sarcoma and osteosarcoma are the two primary types of bone sarcomas. The group of Ewing sarcomas consists of a skin tumor, extraosseous Ewing tumor, PNETs, or peripheral neuroectodermal tumors neuroepitheliomas (the chest wall's PNETs). These malignancies originate from the same kind of stem cell [48]. Soft tissue and bone sarcomas in adults. The majority of uncommon malignancies fall under the category of sarcomas. Bone and soft tissue sarcomas. By the site or kind of tissue that is damaged, they are cancers of the mesenchymal (supporting) tissues. The most prevalent sarcoma, gastrointestinal stromal tumor, or GIST, damages the gastrointestinal tract's wall and is typically classified separately from other sarcomas. Adult soft tissue sarcomas account for more than 80% of sarcomas, with an incidence of 4 per 100,000 people annually in Europe. They are distinct from childhood soft tissue sarcomas., which frequently occur in rare pediatric cancers and have various characteristics, Guidelines, and treatment procedures. For more information, Consult the SIOPE Strategic Plan and the European Society for Paediatric Oncology [49]. About 15% of sarcomas in Europe are these, which are less common than adult soft tissue sarcomas. The most prevalent kinds osteosarcoma and Ewing sarcoma, which are featured in this publication because the treatment strategies used are similar to those employed for adults. Teenagers and young adults are the most susceptible to these types. The most frequent adult bone sarcoma is chondrosarcoma Undifferentiated pleomorphic Sarcomas of the Bone. A few other bone sarcomas are chordomas, giant cell tumors of the bone, and undifferentiated pleomorphic sarcomas of the bone (UPS). For children and adolescents with bone sarcomas, The European Standards of Care for Children with Cancer also apply [50].

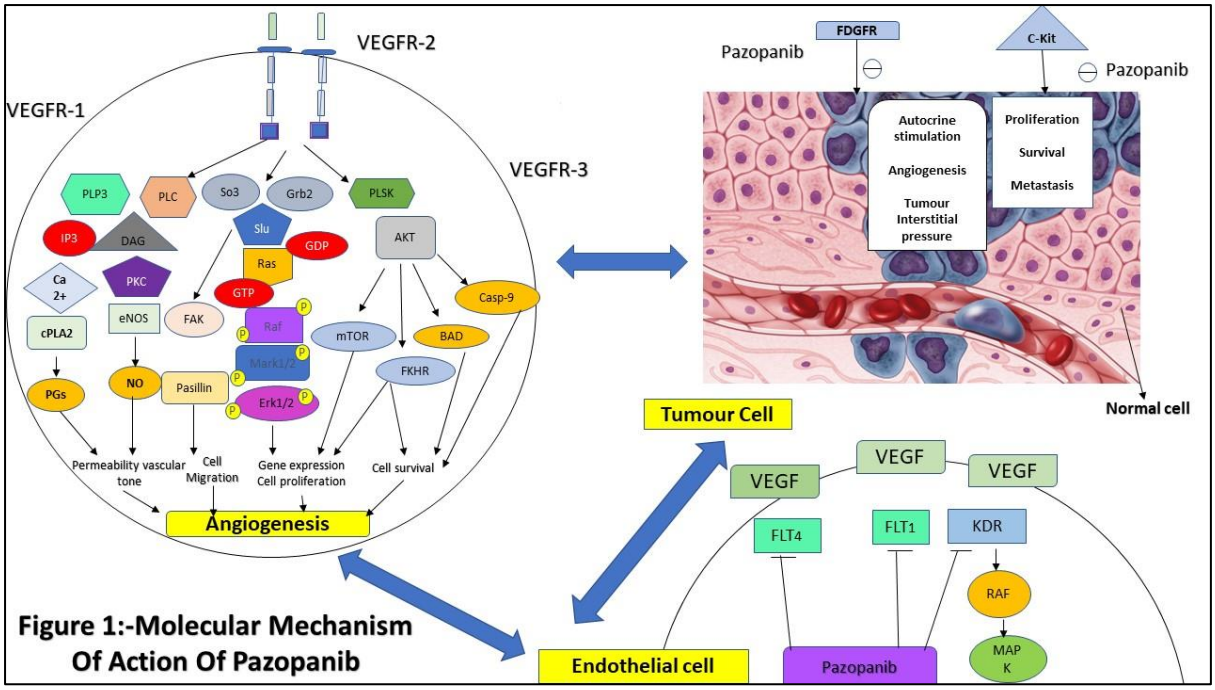

Figure1. Molecular mechanism of action of pazopanib

4. Diagnosis

Due to the rarity of sarcomas, the wide variety of forms, and the frequently ambiguous symptoms, most primary care physicians only occasionally encounter a patient who has sarcoma. A benign diagnosis may also outnumber a sarcoma diagnosis by a factor of 100. Delays in referrals and diagnosis may occur from this. Making the proper diagnosis of sarcomas requires the expertise of radiologists and pathologists who specialize in sarcomas, although they often work in a few numbers of centers. Non-expert surgical biopsies may result in issues, problems with following therapies, and even the spread of the tumor [51]. The ECCO expert panel emphasizes that only sarcoma centers or pediatric cancer centers with experience treating sarcomas should be used for diagnosis. In the second reading, it was discovered that more than 40% of initial histological diagnoses had been altered, possibly influencing different treatment options [52]. In conclusion, a patient who is not diagnosed at a sarcoma center may suffer serious repercussions, such as missing the possibility of receiving a prompt diagnosis of a condition that may be treatable and avoiding more invasive surgery [53].

5. Treatment soft tissue sarcoma

Soft tissue sarcomas are a diverse group of rare malignancies that originate from mesenchymal tissue, including muscles, fat, nerves, blood vessels, and other connective tissues. Treatment for soft tissue sarcoma typically involves a multidisciplinary approach, considering factors such as tumor location, size, grade, and patient's overall health. Surgery is often the primary treatment for localized soft tissue sarcomas, aiming to remove the tumor with negative margins while preserving surrounding healthy tissue. In cases where surgery alone is insufficient, radiation therapy may be used preoperatively to shrink the tumor or postoperatively to eliminate residual cancer cells. For advanced or metastatic soft tissue sarcomas that cannot be effectively treated with surgery or radiation, systemic therapy becomes the mainstay of treatment. Chemotherapy has historically been a cornerstone of systemic treatment for soft

tissue sarcomas, although its efficacy varies depending on the subtype of sarcoma (see Table 1).

Table 1: Treatment for soft tissue sarcoma

SR NO	GENE	SNP	CANCER TYPE	THERAPY	TOXICITY	REFERENCE
1	SLC22A16	rs714368 rs6907567 rs723685	ASTS	Doxorubicin	decreased the frequency of grade 3–4 AE (rs723685)	[54]
2	ABCB1	rs1128503	ASTS	Trabectedin	decreased risk of severe hepatic cytolysis	[55]
		rs2032582	ASTS	Trabectedin	decreased risk of overall hepatotoxicity	
3	ABCC2	rs717620 rs8187707 rs8187710	LPS	Trabectedin	irreversible hepatotoxicity	[56]
		rs2273697	ASTS	Trabectedin	increased risk of hepatic cytolysis	
		rs17222723	ASTS	Trabectedin	decreased risk of hepatic cytolysis	
4	ABCC3	rs2072365	ASTS	Trabectedin	higher potential for severe cytolysis and total hepatotoxicity	[57]
5	ABCC4	rs9516519	ASTS	Trabectedin	overall hepatotoxicity risk is reduced	[58]

6	ABCG2	rs7699188	ASTS	Trabectedin	Hepatic cytolysis is more likely to occur.	[59]
7	CYP3A5	rs779746	ASTS	Trabectedin	grade 3/4 hepatic incident is more likely to occur.	[60]
8	ITGA	rs1126643	STS	Apatinib	spontaneous pneumothorax and surgical wound complications	[61]

Abbreviations: LPS = liposarcoma; ASTS = advanced soft tissue sarcoma; AE = adverse event; SNP = single nucleotide polymorphism.

6. Pazopanib

To treat advanced renal cell carcinoma, the medication pazopanib (Votrient®) is prescribed. Vascular endothelial growth factor receptors (VEGFR-1, VEGFR-2), and VEGFR-3), platelet-derived growth factor receptors, and stem cell growth factor receptor (c-Kit) are the targets of this drug's tyrosine kinase inhibitor class i.e pazopanib as shown in figure 1 [62]. According to the most recent dosing recommendations, a starting dose of 800 mg once daily is indicated for treatment [63]. Because pazopanib is taken by up to 40–50% of patients with renal cancer, there have been worries about hepatotoxicity with this medication. in clinical trials had elevated blood transaminases and bilirubin [64]. the US Food and Drug Administration (FDA) mandated a black box alert in 2012 [65-68]. The anticancer and antiangiogenic efficacy of pazopanib in preclinical tests using mice xenograft models with multiple myeloma cell models is reliant on concentration, requiring a steady-state plasma concentration of >40 mol/l (= 17.5 mg/L). Pazopanib's effectiveness in treating patients with metastatic RCC was connected to pazopanib C trough of 15 mg/L in a phase I dose-escalating experiment, The patients received dosages ranging from 50 mg three times weekly to 2000 mg OD and 300-400 mg BID [69]. Patients received 800 mg or 300 mg BID, who showed a clinical response. Although MTD (maximum tolerable dose) was not reached, At the suggested dose of 800 mg OD, the exposure to pazopanib did not increase with predefined dose decreases in case of unacceptable toxicity. Active metabolites of pazopanib account for a further 6% of all drug exposure. An additional 6% of pazopanib exposure is through its active metabolites [70].

7. Clinical response thresholds

7.1 Exposure-response relationships

There is clinical research on the relationship between pazopanib's exposure effectiveness [71]. Pazopanib threshold C trough >20.5 mg/L was identified by Suttle et al as being associated showed a substantial increase in the median PFS in RCC patients [72]. Patients below this

cutoff demonstrated similar efficacy to placebo. This threshold was independently confirmed by Verheijen et al, and it roughly corresponds to the results of the preclinical/early-phase trials. Although there were variations in reaction at the same threshold for STS patients, The difference was not statistically significant. This may be because there were fewer patients and a smaller impact size in STS patients in comparison to m RCC, so even though it was less durable, the same threshold may still be appropriate for STS patients. pazopanib trough levels have been linked to both survival and response rates (as determined by the RECIST criteria); 11 of the remaining 24 RCC patients out of 27 patients had an OR, but of the remaining 24 patients, none of the three individuals with a pazopanib C trough of 20.5 mg/L out of 27 RCC patients [73].

7.2 Relation between toxicity and exposure

It has also been proven that exposure and toxicity are related, demonstrating that an increase in pazopanib C trough is linked to an increase in the frequency of adverse events [74-88]. In two investigations (n = 205), it was determined that individuals with the highest levels of pazopanib C trough > 46 mg/L rate of adverse events (AEs), particularly those with hand-foot syndrome and hypertension (all grades). Recently, Noda et al (n = 27) determined a somewhat equivalent upper threshold of 50.3 mg/L for grade 3 toxicity. The results were most convincing for fatigue, anorexia, and hypertension [89].

8. Future Prospects

Pazopanib represents a significant advancement in the realm of targeted cancer therapy, offering a potent monotherapy option for the treatment of certain types of cancer [90]. As a multitargeted tyrosine kinase inhibitor, pazopanib demonstrates efficacy in inhibiting the activity of various receptors involved in tumor angiogenesis, growth, and progression. This mechanism of action makes pazopanib particularly effective in targeting specific mutations and tumors, offering a tailored approach to cancer treatment [91]. One of the key strengths of pazopanib lies in its ability to target specific molecular pathways implicated in cancer development and progression [92]. By inhibiting vascular endothelial growth factor receptors (VEGFRs), platelet-derived growth factor receptors (PDGFRs), and other tyrosine kinases, pazopanib disrupts the signaling cascades that promote tumor growth and angiogenesis [93]. This targeted approach not only slows down tumor progression but also helps in shrinking existing tumors, thereby providing tangible benefits for patients with advanced or metastatic disease [94]. Clinical studies have demonstrated the efficacy of pazopanib across various cancer types, including renal cell carcinoma (RCC), soft tissue sarcoma (STS), and ovarian cancer. In RCC, pazopanib has shown superior progression-free survival compared to placebo, leading to its approval as a first-line treatment for advanced RCC [95]. Similarly, in STS, pazopanib has demonstrated efficacy in prolonging progression-free survival, particularly in patients with leiomyosarcoma and synovial sarcoma. These findings underscore the potential of pazopanib as a valuable treatment option for specific subtypes of cancer where targeted therapy is warranted [96]. Importantly, pazopanib offers a favorable safety profile, with manageable adverse effects that can be effectively addressed with dose modifications or supportive care measures [97]. Common side effects of pazopanib include hypertension, fatigue, diarrhea, and elevated liver enzymes, which are generally mild to moderate in severity [98]. By closely monitoring patients and implementing appropriate management strategies, healthcare providers can mitigate these side effects and optimize treatment outcomes. The

development of pazopanib highlights the paradigm shift towards precision medicine in oncology, where treatment decisions are guided by the molecular characteristics of individual tumors. Through molecular profiling and genomic analysis, oncologists can identify specific mutations and alterations driving tumor growth, allowing for the selection of targeted therapies such as pazopanib that are most likely to be effective [99]. This personalized approach not only improves treatment efficacy but also minimizes unnecessary exposure to toxicities associated with conventional chemotherapy. Looking ahead, ongoing research efforts are focused on exploring the potential of pazopanib in combination with other targeted agents or immunotherapies to further enhance treatment outcomes. Combinatorial approaches hold promise for overcoming resistance mechanisms and maximizing the therapeutic benefit of pazopanib across a broader spectrum of cancer types [100]. Additionally, biomarker-driven clinical trials are underway to identify predictive markers of response to pazopanib, facilitating the identification of patients who are most likely to benefit from this targeted therapy. In conclusion, pazopanib represents a milestone in the field of precision oncology, offering an effective monotherapy option for the treatment of specific mutations and tumors. By selectively targeting key molecular pathways implicated in cancer pathogenesis, pazopanib demonstrates efficacy across various cancer types while minimizing systemic toxicity. With ongoing research and clinical advancements, pazopanib holds promise as a cornerstone of targeted cancer therapy, paving the way for improved outcomes and personalized treatment strategies for patients facing this complex disease [101].

9. Conclusion

We advise setting a target exposure threshold of >20.5 mg/L for pazopanib C trough because multiple clinical trials have shown a correlation between pazopanib C trough >20.5 mg/L and a notable increase in median PFS. Pazopanib C trough values >46 mg/L patients report experiencing more toxicity. Due to their apparent inability to tolerate the treatment's negative effects or to get a significant benefit from it. Therefore, there is no agreed-upon standard of care, and there are no definitive rules for them to take care of patients with low PS. PFS (progression-free survival) and overall survival rates have significantly improved in first-line therapy trials for an RCC (OS). Tyrosine kinase inhibitors (TKIs) targeting 1-4 VEGFRs and, more recently, testing of either two immune checkpoint inhibitors (ICI) or a mix of one ICI and a TKI. Most of these trials, however, excluded RCC ECOG PS 2 patients, Karnofsky PS 70% of patients, and just 1 included patients using ECOG PS 0-23. Therefore, there is a lack of information on the therapies' tolerance and effectiveness for RCC patients with low PS. The TKI pazopanib targets the signaling pathways involved in the formation of tumors as well as VEGFR-1, -2, and -3. 10 The recommended treatment for an RCC at the time was sunitinib, a VEGFR-targeting TKI. was shown to have a shorter PFS than pazopanib in a significant phase III trial in patients with an RCC and PS 0–1 [86]. The same trial also showed that pazopanib had improved health-related quality of life (QoL) ratings and was better tolerated than sunitinib. Poor PS is seen in between 13% and 29% of all RCC patients [87,88]. To close this knowledge gap and establish a higher standard of care for these patients, the Pazo2 study was developed. Pazo2's objective was to evaluate the drug's effectiveness and tolerability. The first-line use of Pazopanib therapy for RCC patients with ECOG PS2. The long-standing persistent need for effective novel treatments for these uncommon diseases has been addressed by pazopanib's successful clinical development as a treatment for advanced STS. However, based on formally

documented clinical trial data, only a small proportion of the STS population's patients will benefit from treatment, and in many cases, the benefit's duration would be brief. Until yet, baseline clinicopathological factors that improve pazopanib benefit have not been identified in data from prospective pazopanib studies' subgroup analyses. Additionally, the scant Translational research that has looked at circulating or tumor-based biomarkers has not yet provided meaningful and reliable potential biomarkers. Numerous biomolecular profiling data points point to the presence of intrinsic biological subgroups within particular STS histocytes. Additionally, it has been shown that biological characteristics including enhanced chromosomal instability occur in a percentage of tumors across different Similar clinical signs and are associated with STS subtypes [90–92]. An interesting direction for biomarker research is the evaluation of differing treatment results between such physiologically characterized pazopanib-treated cohorts' STS subgroups. improved discriminatory trial endpoints and assistance in the identification and validation of potential imaging surrogate markers for survival could lead to the early diagnosis of clinical effects. The exact mechanism(s) by which When used in STS, pazopanib has an anticancer effect. changes across and within various STS subtypes are currently unknown. Furthermore, pazopanib resistance is frequently developed, even in individuals who initially showed a clear benefit from treatment.

Acknowledgments

The authors would like to acknowledge the management of colleges and universities of all authors for overall support in carrying out the review work.

Competing interest statement

The authors declare no conflict of interest.

Disclaimer

None

List of abbreviations

DNA	Deoxyribonucleic acid
SSB	Single-strand breaks
DSB	Double-strand breaks
GBM	Glioblastoma
MRI	Magnetic resonance imaging
CT	Computed tomography
GI	Gastrointestinal
STS	Soft tissue sarcomas

References

1. Adamu, A., Li, S., Gao, F., Xue, G., 2024. The role of neuroinflammation in neurodegenerative diseases: current understanding and future therapeutic targets. Front. Aging Neurosci. 16, 1347987.
2. Al-Khateeb, Z.F., Boumenar, H., Adebimpe, J., Shekerzade, S., Henson, S.M., Tremoleda, J.L., Michael-Titus, A.T., 2024. The cellular senescence response and neuroinflammation in juvenile mice following controlled cortical impact and repetitive mild traumatic brain injury. Exp. Neurol. 374, 114714. https://doi.org/https://doi.org/10.1016/j.expneurol.2024.114714
3. Alqahtani, T., Deore, S.L., Kide, A.A., Shende, B.A., Sharma, R., Dadarao Chakole, R., Nemade, L.S., Kishor Kale, N., Borah, S., Shrikant Deokar, S., Behera, A., Dhawal Bhandari, D., Gaikwad, N., Kalam Azad, A., Ghosh, A., 2023. Mitochondrial dysfunction and oxidative stress in Alzheimer's disease, and Parkinson's disease, Huntington's disease and Amyotrophic Lateral Sclerosis -An updated review. Mitochondrion 71, 83–92. https://doi.org/https://doi.org/10.1016/j.mito.2023.05.007
4. Arroyo, D.S., Gaviglio, E.A., Peralta Ramos, J.M., Bussi, C., Rodriguez-Galan, M.C., Iribarren, P., 2014. Autophagy in inflammation, infection, neurodegeneration and cancer. Int. Immunopharmacol. 18, 55–65. https://doi.org/https://doi.org/10.1016/j.intimp.2013.11.001
5. Ashique, S., Bhowmick, M., Pal, R., Khatoon, H., Kumar, P., Sharma, H., Garg, A., Kumar, S., Das, U., 2024a. Multi drug resistance in Colorectal Cancer- approaches to overcome, advancements and future success. Adv. Cancer Biol. - Metastasis 10, 100114. https://doi.org/https://doi.org/10.1016/j.adcanc.2024.100114
6. Ashique, S., Pal, R., Sharma, H., Mishra, N., Garg, A., 2024b. Unraveling the Emerging Niche Role of Extracellular Vesicles (EVs) in Traumatic Brain Injury (TBI). CNS Neurol. Disord. Drug Targets.
7. Asthana, P., Wong, H.L.X., 2024. Preventing obesity, insulin resistance and type 2 diabetes by targeting MT1-MMP. Biochim. Biophys. Acta - Mol. Basis Dis. 1870, 167081. https://doi.org/https://doi.org/10.1016/j.bbadis.2024.167081
8. Bae, S., Ullah, I., Beloor, J., Lim, J., Chung, K., Yi, Y., Kang, E., Yun, G., Rhim, T., Lee, S.-K., 2024. Blocking Fas-signaling in adipocytes and hepatocytes prevents obesity-associated inflammation, insulin resistance, and hepatosteatosis. J. Ind. Eng. Chem. https://doi.org/https://doi.org/10.1016/j.jiec.2024.01.055
9. Barros, C., Fernandes, A., 2021. Linking Cognitive Impairment to Neuroinflammation in Multiple Sclerosis using neuroimaging tools. Mult. Scler. Relat. Disord. 47, 102622. https://doi.org/https://doi.org/10.1016/j.msard.2020.102622
10. Bhandari, M., Sharma, S., Mishra, R., Nogai, L., Bajaj, M., Pathak, R., 2022. Geography And The Therapeutic Effect Of Matcha Tea In Drinks. J. Pharm. Negat. Results 5094–5099.
11. Bhattacharya, V., Kumar Bhatt, A., Sharma, H., Garg, S., Chaurasia, G., Akram, W., Sharma, K., Mandal, S., n.d. Optimization of formulation by box behnken and invitro studies of emulsified gel containing zaltoprofen for the management of arthritis. Eur. Chem. Bull 2023, 11734–11744.

12. Bhuiyan, P., Sun, Z., Chen, Y., Qian, Y., 2023. Peripheral surgery triggers mast cells activation: Focusing on neuroinflammation. Behav. Brain Res. 452, 114593. https://doi.org/https://doi.org/10.1016/j.bbr.2023.114593
13. Bhusal, A., Kim, J.-H., Kim, S.-C., Hwang, E.M., Ryu, H., Ali, M.S., Park, S.-C., Lee, W.-H., Suk, K., 2024. The microglial innate immune protein PGLYRP1 mediates neuroinflammation and consequent behavioral changes. Cell Rep. 43, 113813. https://doi.org/https://doi.org/10.1016/j.celrep.2024.113813
14. Bonam, S.R., Mastrippolito, D., Georgel, P., Muller, S., 2024. Pharmacological targets at the lysosomal autophagy–NLRP3 inflammasome crossroads. Trends Pharmacol. Sci. 45, 81–101. https://doi.org/https://doi.org/10.1016/j.tips.2023.11.005
15. Burtscher, J., Pepe, G., Maharjan, N., Riguet, N., Di Pardo, A., Maglione, V., Millet, G.P., 2023. Sphingolipids and impaired hypoxic stress responses in Huntington disease. Prog. Lipid Res. 90, 101224. https://doi.org/https://doi.org/10.1016/j.plipres.2023.101224
16. Chandra, P., Ali, Z., Fatima, N., Sharma, H., Sachan, N., Sharma, K.K., Verma, A., 2024. Shankhpushpi (Convolvulus pluricaulis): Exploring its Cognitive Enhancing Mechanisms and Therapeutic Potential in Neurodegenerative Disorders. Curr. Bioact. Compd. 20. https://doi.org/10.2174/0115734072292339240416095600
17. Chandra, P., Kaleem, M., Sachan, N., Pathak, R., Alanazi, A.S., Alsaif, N.A., Alsanea, S., Alsuwayt, B., Alanazi, M.M., Kabra, A., 2023a. Gastroprotective evaluation of Medicago sativa L.(Fabaceae) on diabetic rats. Saudi Pharm. J. 31, 101815.
18. Chandra, P., Sachan, N., Pathak, R., Pal, D., 2023b. Medicinal Plants Against Vesicular Stomatitis Virus (VSV) Infections: Ethnopharmacology, Chemistry, and Clinical and Preclinical Studies, in: Anti-Viral Metabolites from Medicinal Plants. Springer, pp. 603–638.
19. Das, S., Mukherjee, T., Mohanty, S., Nayak, N., Mal, P., Ashique, S., Pal, R., Mohanto, S., Sharma, H., 2024. Impact of NF-κB Signaling and Sirtuin-1 Protein for Targeted Inflammatory Intervention. Curr. Pharm. Biotechnol. 25. https://doi.org/10.2174/0113892010301469240409082212
20. De Mario, A., Quintana-Cabrera, R., Martinvalet, D., Giacomello, M., 2017. (Neuro)degenerated Mitochondria-ER contacts. Biochem. Biophys. Res. Commun. 483, 1096–1109. https://doi.org/https://doi.org/10.1016/j.bbrc.2016.07.056
21. Domínguez-Rivas, E., Ávila-Muñoz, E., Schwarzacher, S.W., Zepeda, A., 2021. Adult hippocampal neurogenesis in the context of lipopolysaccharide-induced neuroinflammation: A molecular, cellular and behavioral review. Brain. Behav. Immun. 97, 286–302. https://doi.org/https://doi.org/10.1016/j.bbi.2021.06.014
22. Duarte, A.I., Santos, M.S., Oliveira, C.R., Moreira, P.I., 2018. Brain insulin signalling, glucose metabolism and females' reproductive aging: A dangerous triad in Alzheimer's disease. Neuropharmacology 136, 223–242. https://doi.org/https://doi.org/10.1016/j.neuropharm.2018.01.044
23. Dwivedi, M., Jha, K.K., Pandey, S., Sachan, A., Sharma, H., Dwivedi, S.K., n.d. Formulation and Evaluation of Herbal Medicated Chocolate in Treatment of Intestinal Worms and Related Problems.

24. Ertuglu, L.A., Sahinoz, M., Alsouqi, A., Deger, S.M., Guide, A., Stewart, T.G., Pike, M., Robinson-Cohen, C., Akwo, E., Pridmore, M., Crescenzi, R., Madhur, M.S., Harrison, D.G., Luft, F.C., Titze, J., Ikizler, T.A., 2023. High tissue-sodium associates with systemic inflammation and insulin resistance in obese individuals. Nutr. Metab. Cardiovasc. Dis. 33, 1398–1406. https://doi.org/https://doi.org/10.1016/j.numecd.2023.03.024
25. Fettig, N.M., Osborne, L.C., 2021. Direct and indirect effects of microbiota-derived metabolites on neuroinflammation in multiple sclerosis. Microbes Infect. 23, 104814. https://doi.org/https://doi.org/10.1016/j.micinf.2021.104814
26. Fominykh, V., Shadrin, A.A., Jaholkowski, P.P., Bahrami, S., Athanasiu, L., Wightman, D.P., Uffelmann, E., Posthuma, D., Selbæk, G., Dale, A.M., Djurovic, S., Frei, O., Andreassen, O.A., 2023. Shared genetic loci between Alzheimer's disease and multiple sclerosis: Crossroads between neurodegeneration and immune system. Neurobiol. Dis. 183, 106174. https://doi.org/https://doi.org/10.1016/j.nbd.2023.106174
27. Gan, H., Ma, Q., Hao, W., Yang, N., Chen, Z.-S., Deng, L., Chen, J., 2024. Targeting autophagy to counteract neuroinflammation: A novel antidepressant strategy. Pharmacol. Res. 202, 107112. https://doi.org/https://doi.org/10.1016/j.phrs.2024.107112
28. Ghosh, P., Singh, R., Ganeshpurkar, A., Pokle, A.V., Singh, R. bhushan, Singh, S.K., Kumar, A., 2021. Cellular and molecular influencers of neuroinflammation in Alzheimer's disease: Recent concepts & roles. Neurochem. Int. 151, 105212. https://doi.org/https://doi.org/10.1016/j.neuint.2021.105212
29. Gonzalez-Lima, F., Barksdale, B.R., Rojas, J.C., 2014. Mitochondrial respiration as a target for neuroprotection and cognitive enhancement. Biochem. Pharmacol. 88, 584–593. https://doi.org/https://doi.org/10.1016/j.bcp.2013.11.010
30. Goyal, D., Ali, S.A., Singh, R.K., 2021. Emerging role of gut microbiota in modulation of neuroinflammation and neurodegeneration with emphasis on Alzheimer's disease. Prog. Neuro-Psychopharmacology Biol. Psychiatry 106, 110112. https://doi.org/https://doi.org/10.1016/j.pnpbp.2020.110112
31. Guzman-Martinez, L., Maccioni, R.B., Andrade, V., Navarrete, L.P., Pastor, M.G., Ramos-Escobar, N., 2019. Neuroinflammation as a common feature of neurodegenerative disorders. Front. Pharmacol. 10, 1008.
32. Halagali, P., Inamdar, A., Singh, J., Anand, A., Sadhu, P., Pathak, R., Sharma, H., Biswas, D., 2024. Phytochemicals, Herbal Extracts, and Dietary Supplements for Metabolic Disease Management. Endocrine, Metab. Immune Disord. - Drug Targets 24. https://doi.org/10.2174/0118715303287911240409055710
33. Himanshu Sharma, Pathak, R., Saxena, D., Kumar, N., 2022. Emerging role of non-coding RNA'S: Human health and diseases. GIS J. 9, 2022–2050.
34. Huang, A., Ji, L., Li, Yamei, Li, Yufeng, Yu, Q., 2023. Gut microbiome plays a vital role in post-stroke injury repair by mediating neuroinflammation. Int. Immunopharmacol. 118, 110126. https://doi.org/https://doi.org/10.1016/j.intimp.2023.110126

35. Kieffer, D.A., Medici, V., 2017. Wilson disease: At the crossroads between genetics and epigenetics—A review of the evidence. Liver Res. 1, 121–130. https://doi.org/https://doi.org/10.1016/j.livres.2017.08.003
36. Kleiboeker, B., He, A., Tan, M., Lu, D., Hu, D., Liu, X., Goodarzi, P., Hsu, F.-F., Razani, B., Semenkovich, C.F., Lodhi, I.J., 2024. Adipose tissue peroxisomal lipid synthesis orchestrates obesity and insulin resistance through LXR-dependent lipogenesis. Mol. Metab. 82, 101913. https://doi.org/https://doi.org/10.1016/j.molmet.2024.101913
37. Kumar, P., Pandey, S., Ahmad, F., Verma, A., Sharma, H., Ashique, S., Bhattacharyya, S., Bhattacharyya, I., Kumar, S., Mishra, N., Garg, A., 2023. Carbon Nanotubes: A Targeted Drug Delivery against Cancer Cell. Curr. Nanosci. 9, 1–31. https://doi.org/10.2174/0115734137271865231105070727
38. Kumar, P., Sharma, H., Singh, A., Durgapal, S., Kukreti, G., Bhowmick, M., Bhowmick, P., Ashique, S., 2024a. Targeting the Interplay of Proteins through PROTACs for Management Cancer and Associated Disorders. Curr. Cancer Ther. Rev. 20. https://doi.org/10.2174/0115733947304806240417092449
39. Kumar, P., Sharma, H., Singh, A., Pandey, S.N., Chandra, P., 2024b. Correlation Between Exosomes and Neuro-inflammation in Various Brain Disorders BT - Exosomes Based Drug Delivery Strategies for Brain Disorders, in: Mishra, N., Ashique, S., Garg, A., Chithravel, V., Anand, K. (Eds.), . Springer Nature Singapore, Singapore, pp. 273–302. https://doi.org/10.1007/978-981-99-8373-5_11
40. Kumari, S., Dhapola, R., Sharma, P., Singh, S.K., Reddy, D.H., 2023. Implicative role of cytokines in neuroinflammation mediated AD and associated signaling pathways: Current progress in molecular signaling and therapeutics. Ageing Res. Rev. 92, 102098. https://doi.org/https://doi.org/10.1016/j.arr.2023.102098
41. Lacroix, C., Guilhaumou, R., Micallef, J., Bruneteau, G., Desnuelle, C., Blin, O., 2023. Cannabis for the treatment of amyotrophic lateral sclerosis: What is the patients' view? Rev. Neurol. (Paris). 179, 967–974. https://doi.org/https://doi.org/10.1016/j.neurol.2023.03.018
42. Lee, M.Y., Kim, M., 2024. Effects of Red ginseng on neuroinflammation in neurodegenerative diseases. J. Ginseng Res. 48, 20–30. https://doi.org/https://doi.org/10.1016/j.jgr.2023.08.003
43. Levy Nogueira, M., Epelbaum, S., Steyaert, J.-M., Dubois, B., Schwartz, L., 2016. Mechanical stress models of Alzheimer's disease pathology. Alzheimer's Dement. 12, 324–333. https://doi.org/https://doi.org/10.1016/j.jalz.2015.10.005
44. Li, Q., Jia, C., Wu, H., Liao, Y., Yang, K., Li, S., Zhang, J., Wang, J., Li, G., Guan, F., Leung, E., Yuan, Z., Hua, Q., Pan, R.-Y., 2022. Nao Tan Qing ameliorates Alzheimer's disease-like pathology by regulating glycolipid metabolism and neuroinflammation: A network pharmacology analysis and biological validation. Pharmacol. Res. 185, 106489. https://doi.org/https://doi.org/10.1016/j.phrs.2022.106489
45. Li, Y., Hao, J., Kong, X., Yuan, W., Shen, Y., Hui, Z., Lu, X., 2024. Rabeprazole mitigates obesity-induced chronic inflammation and insulin resistance associated with increased M2-type macrophage polarization. Biochim. Biophys. Acta - Mol. Basis Dis. 1870, 167142. https://doi.org/https://doi.org/10.1016/j.bbadis.2024.167142

46. Liu, Y., Yang, W., Xue, J., Chen, J., Liu, S., Zhang, S., Zhang, X., Gu, X., Dong, Y., Qiu, P., 2023. Neuroinflammation: The central enabler of postoperative cognitive dysfunction. Biomed. Pharmacother. 167, 115582. https://doi.org/https://doi.org/10.1016/j.biopha.2023.115582
47. Ly, M., Yu, G.Z., Mian, A., Cramer, A., Meysami, S., Merrill, D.A., Samara, A., Eisenstein, S.A., Hershey, T., Babulal, G.M., Lenze, E.J., Morris, J.C., Benzinger, T.L.S., Raji, C.A., 2023. Neuroinflammation: A Modifiable Pathway Linking Obesity, Alzheimer's disease, and Depression. Am. J. Geriatr. Psychiatry 31, 853–866. https://doi.org/https://doi.org/10.1016/j.jagp.2023.06.001
48. Maestri, A., Garagnani, P., Pedrelli, M., Hagberg, C.E., Parini, P., Ehrenborg, E., 2024. Lipid droplets, autophagy, and ageing: A cell-specific tale. Ageing Res. Rev. 94, 102194. https://doi.org/https://doi.org/10.1016/j.arr.2024.102194
49. Mahaman, Y.A.R., Embaye, K.S., Huang, F., Li, L., Zhu, F., Wang, J.-Z., Liu, R., Feng, J., Wang, X., 2022. Biomarkers used in Alzheimer's disease diagnosis, treatment, and prevention. Ageing Res. Rev. 74, 101544. https://doi.org/https://doi.org/10.1016/j.arr.2021.101544
50. Manju Koli, 2023. Formulation And Evaluation Of Berberine Hydrochloride Film Coated Tablet. J. Pharm. Negat. Results 3439–3449. https://doi.org/10.47750/pnr.2023.14.02.403
51. Meng, L., Li, Y., Liu, Congcong, Zhang, G., Chen, J., Xiong, M., Pan, L., Zhang, X., Chen, G., Xiong, J., Liu, Chaoyang, Xu, X., Bu, L., Zhang, Zhaohui, Zhang, Zhentao, 2023. Islet amyloid polypeptide triggers α-synuclein pathology in Parkinson's disease. Prog. Neurobiol. 226, 102462. https://doi.org/https://doi.org/10.1016/j.pneurobio.2023.102462
52. Mezouar, S., Chantran, Y., Michel, J., Fabre, A., Dubus, J.-C., Leone, M., Sereme, Y., Mège, J.-L., Ranque, S., Desnues, B., Chanez, P., Vitte, J., 2018. Microbiome and the immune system: From a healthy steady-state to allergy associated disruption. Hum. Microbiome J. 10, 11–20. https://doi.org/https://doi.org/10.1016/j.humic.2018.10.001
53. Miao, L., Zhang, X., Zhang, H., Cheong, M.S., Chen, X., Farag, M.A., Cheang, W.S., Xiao, J., 2024. Baicalin ameliorates insulin resistance and regulates hepatic glucose metabolism via activating insulin signaling pathway in obese pre-diabetic mice. Phytomedicine 124, 155296. https://doi.org/https://doi.org/10.1016/j.phymed.2023.155296
54. Mohan, S., Alhazmi, H.A., Hassani, R., Khuwaja, G., Maheshkumar, V.P., Aldahish, A., Chidambaram, K., 2024. Role of ferroptosis pathways in neuroinflammation and neurological disorders: From pathogenesis to treatment. Heliyon 10, e24786. https://doi.org/https://doi.org/10.1016/j.heliyon.2024.e24786
55. Muwanigwa, M.N., Modamio-Chamarro, J., Antony, P.M.A., Gomez-Giro, G., Krüger, R., Bolognin, S., Schwamborn, J.C., 2024. Alpha-synuclein pathology is associated with astrocyte senescence in a midbrain organoid model of familial Parkinson's disease. Mol. Cell. Neurosci. 128, 103919. https://doi.org/https://doi.org/10.1016/j.mcn.2024.103919
56. Nordström, E., Eriksson, F., Sigvardson, J., Johannesson, M., Kasrayan, A., Jones-Kostalla, M., Appelkvist, P., Söderberg, L., Nygren, P., Blom, M., Rachalski, A.,

Nordenankar, K., Zachrisson, O., Amandius, E., Osswald, G., Moge, M., Ingelsson, M., Bergström, J., Lannfelt, L., Möller, C., Giorgetti, M., Fälting, J., 2021. ABBV-0805, a novel antibody selective for soluble aggregated α-synuclein, prolongs lifespan and prevents buildup of α-synuclein pathology in mouse models of Parkinson's disease. Neurobiol. Dis. 161, 105543. https://doi.org/https://doi.org/10.1016/j.nbd.2021.105543

57. Pandey Priya, Kuma Nitin, Kaur Teljinder, Saini Shalini, S.H., 2022. Antidiabetic activity of caesalpinia bonducella leavess of hydro alcoholic extracts in albino rats. YMER 7, 840–846.
58. Pascale, A., Marchesi, N., Govoni, S., Barbieri, A., 2020. Targeting the microbiota in pharmacology of psychiatric disorders. Pharmacol. Res. 157, 104856. https://doi.org/https://doi.org/10.1016/j.phrs.2020.104856
59. Pathak, Rashmi & Sharma, Himanshu & Nogai, Lipi & Bhandari, Maulshree & Koli, Manju & Mishra, Riya & Kumar, N., 2023. A brief review on Pathogenesis, Transmission and Management of Monkeypox virus outbreaks. Bull. Environ. Pharmacol. Life Sci. 12, 244–256.
60. Pathak, R., Pandey, S.P., Chandra, P., 2024. Gastroprotective Effects of Biological Macromolecule: Polysaccharides, in: Macromolecular Symposia. Wiley Online Library, p. 2300122.
61. Pathak, R., Sachan, N., Chandra, P., 2022a. Mechanistic approach towards diabetic neuropathy screening techniques and future challenges: A review. Biomed. Pharmacother. 150, 113025.
62. Pathak, R., Sachan, N., Kabra, A., Alanazi, A.S., Alanazi, M.M., Alsaif, N.A., Chandra, P., 2023. Isolation, characterization, development and evaluation of phytoconstituent based formulation for diabetic neuropathy. Saudi Pharm. J. 31, 101687.
63. Pathak, R., Sharma, H., 2021. A review on medicinal uses of Cinnamomum verum (Cinnamon). J. Drug Deliv. Ther. 11, 161–166.
64. Pathak, R., Sharma, H., Kumar, N., 2022b. A Brief Review on Anthocephalus cadamba. Acta Sci. Pharmacol. 3.
65. Paul, S., Bhardwaj, J., Binukumar, B.K., 2024. Cdk5-mediated oligodendrocyte myelin breakdown and neuroinflammation: Implications for the link between Type 2 Diabetes and Alzheimer's disease. Biochim. Biophys. Acta - Mol. Basis Dis. 1870, 166986. https://doi.org/https://doi.org/10.1016/j.bbadis.2023.166986
66. Peng, Z., Li, X.-J., Zhou, Y., Zhang, J.-T., Zhu, Q., Sun, J.-Q., Hang, C.-H., Li, W., Zhang, Q.-R., Zhuang, Z., 2024. Hydrogen exerts neuroprotective effects after subarachnoid hemorrhage by attenuating neuronal ferroptosis and inhibiting neuroinflammation. Free Radic. Biol. Med. 215, 79–93. https://doi.org/https://doi.org/10.1016/j.freeradbiomed.2024.02.028
67. Pratap Singh, L., Gugulothu, S., Perusomula, R., Mishra, A., Durga Bhavani, P., Singh, S., Sharma, H., Dwivedi, M., 2023. Synthesis of Some Tetrazole and Thiazolidine-4-One Derivatives of Schiff base by using Ionic Liquids as Catalyst and Evaluation of their Antifungal and Antibacterial Activity. Bull 6247–6263.
68. Prowse, N., Hayley, S., 2021. Microglia and BDNF at the crossroads of stressor related disorders: Towards a unique trophic phenotype. Neurosci. Biobehav. Rev. 131, 135–163. https://doi.org/https://doi.org/10.1016/j.neubiorev.2021.09.018

69. Ra, E.A., Kim, M.S., Lee, G., 2023. Optogenetic induction of alpha-synuclein aggregation in human dopaminergic neurons to model Parkinson's disease pathology. STAR Protoc. 4, 102609. https://doi.org/https://doi.org/10.1016/j.xpro.2023.102609
70. Rani, N., Sahu, M., Ambasta, R.K., Kumar, P., 2024. Triaging between post-translational modification of cell cycle regulators and their therapeutics in neurodegenerative diseases. Ageing Res. Rev. 94, 102174. https://doi.org/https://doi.org/10.1016/j.arr.2023.102174
71. Ray, R., Juranek, J.K., Rai, V., 2016. RAGE axis in neuroinflammation, neurodegeneration and its emerging role in the pathogenesis of amyotrophic lateral sclerosis. Neurosci. Biobehav. Rev. 62, 48–55. https://doi.org/https://doi.org/10.1016/j.neubiorev.2015.12.006
72. Rossi, D., 2015. Astrocyte physiopathology: At the crossroads of intercellular networking, inflammation and cell death. Prog. Neurobiol. 130, 86–120. https://doi.org/https://doi.org/10.1016/j.pneurobio.2015.04.003
73. Rust, C., Malan-Muller, S., van den Heuvel, L.L., Tonge, D., Seedat, S., Pretorius, E., Hemmings, S.M.J., 2023. Platelets bridging the gap between gut dysbiosis and neuroinflammation in stress-linked disorders: A narrative review. J. Neuroimmunol. 382, 578155. https://doi.org/https://doi.org/10.1016/j.jneuroim.2023.578155
74. Santamarina, A.B., Mennitti, L. V, de Souza, E.A., Mesquita, L.M. d. S., Noronha, I.H., Vasconcelos, J.R.C., Prado, C.M., Pisani, L.P., 2023. A low-carbohydrate diet with different fatty acids' sources in the treatment of obesity: Impact on insulin resistance and adipogenesis. Clin. Nutr. 42, 2381–2394. https://doi.org/https://doi.org/10.1016/j.clnu.2023.09.024
75. Sharma H, Singh S, J.K., 2020. Treatment and recommendations for homeless patients with hypertension, hyperlipidemia & heart failure-a review. ASIO J. Exp. Pharmacol. Clin. Res. 6, 24–32. https://doi.org/http://doi-ds.org/doilink/07.2020-72295186/
76. Sharma, H., Chandra, P., Verma, A., Pandey, S.N., Kumar, P., Sigh, A., 2023a. Therapeutic approaches of nutraceuticals in the prevention of neurological disorders. Eur. Chem. Bull. 12, 1575 – 1596. https://doi.org/10.48047/ecb/2023.12.si5a.038
77. Sharma, H., Kaushik, M., Goswami, P., Sreevani, S., Chakraborty, A., Ashique, S., Pal, R., 2024a. Role of miRNAs in Brain Development. MicroRNA 13. https://doi.org/10.2174/0122115366287127240322054519
78. Sharma, H., Pande, M., Jha, K.K., Sharma, H., 2020. Hyperuricemia: a risk factor beyond gout. ASIO J. Pharm. Herb. Med. Res. 6, 42–49. https://doi.org/http://doi-ds.org/doilink/06.2020-25164442/
79. Sharma, H., Pathak, R., 2021. A review on preliminary phytochemical screening of Curcuma longa linn. ASIO-JPHMR 7, 24–27. https://doi.org/10.2016-19146535
80. Sharma, H., Pathak, R., Jain, S., Bhandari, M., Mishra, R., Reena, K., Varshney, P., 2023b. Ficus racemosa L: a review on its important medicinal uses, phytochemicals and biological activities. J. Popul. Ther. Clin. Pharmacol. 30, 213–227.
81. Sharma, H., Pathak, R., Kumar, N., Nogai, L., Mishra, R., Bhandari, M., Koli, M., Pandey, P., 2023c. Endocannabinoid System: Role in Depression, Recompense, And Pain Control. J. Surv. Fish. Sci. 10, 2743–2751.

82. Sharma, H., Rachamalla, H.K., Mishra, N., Chandra, P., Pathak, R., Ashique, S., 2024b. Introduction to Exosome and Its Role in Brain Disorders BT - Exosomes Based Drug Delivery Strategies for Brain Disorders, in: Mishra, N., Ashique, S., Garg, A., Chithravel, V., Anand, K. (Eds.), . Springer Nature Singapore, Singapore, pp. 1–35. https://doi.org/10.1007/978-981-99-8373-5_1
83. Sharma, H., Rani, T., Khan, S., 2023d. An insight into neuropathic pain: a systemic and up-to-date review. IJPSR 14, 607–621.
84. Sharma, H., Tyagi, S.J., Chandra, P., Verma, A., Kumar, P., Ashique, S., Hussain, A., 2024c. Role of Exosomes in Parkinson's and Alzheimer's Diseases BT - Exosomes Based Drug Delivery Strategies for Brain Disorders, in: Mishra, N., Ashique, S., Garg, A., Chithravel, V., Anand, K. (Eds.), . Springer Nature Singapore, Singapore, pp. 147–182. https://doi.org/10.1007/978-981-99-8373-5_6
85. Sharma H, C.P., 2024. Effects of natural remedies on memory loss and Alzheimer's disease. Afr.J.Bio.Sc. 6, 187–211. https://doi.org/doi.org/ 10.33472/AFJBS.6.7.2024.187-211
86. Spaas, J., Van der Stede, T., de Jager, S., van de Waterweg Berends, A., Tiane, A., Baelde, H., Baba, S.P., Eckhardt, M., Wolfs, E., Vanmierlo, T., Hellings, N., Eijnde, B.O., Derave, W., 2023. Carnosine synthase deficiency aggravates neuroinflammation in multiple sclerosis. Prog. Neurobiol. 231, 102532. https://doi.org/https://doi.org/10.1016/j.pneurobio.2023.102532
87. Sun, L., Wang, X., Guan, S., Chi, L., Liang, M., Lu, X., Luo, T., 2024. Inhibition of voltage-gated Hv1 alleviates LPS-induced neuroinflammation via regulation of microglial metabolic reprogramming. Int. Immunopharmacol. 127, 111361. https://doi.org/https://doi.org/10.1016/j.intimp.2023.111361
88. Sunila, B.G., Dhanushkumar, T., Dasegowda, K.R., Vasudevan, K., Rambabu, M., 2024. Unraveling the molecular landscape of Ataxia Telangiectasia: Insights into Neuroinflammation, immune dysfunction, and potential therapeutic target. Neurosci. Lett. 828, 137764. https://doi.org/https://doi.org/10.1016/j.neulet.2024.137764
89. Surbhi Sharma, Subhas Chandra Dinda, H.S., 2022. Matrix types drug delivery system for sustained release : A review. ASIO J. Drug Deliv. 6, 1–8.
90. Tan, L.S.Y., Francis, H.M., Lim, C.K., 2021. Exploring the roles of tryptophan metabolism in MS beyond neuroinflammation and neurodegeneration: A paradigm shift to neuropsychiatric symptoms. Brain, Behav. Immun. - Heal. 12, 100201. https://doi.org/https://doi.org/10.1016/j.bbih.2021.100201
91. Tsakiridis, E.E., Morrow, M.R., Desjardins, E.M., Wang, D., Llanos, A., Wang, B., Wade, M.G., Morrison, K.M., Holloway, A.C., Steinberg, G.R., 2023. Effects of the pesticide deltamethrin on high fat diet-induced obesity and insulin resistance in male mice. Food Chem. Toxicol. 176, 113763. https://doi.org/https://doi.org/10.1016/j.fct.2023.113763
92. Udayar, V., Chen, Y., Sidransky, E., Jagasia, R., 2022. Lysosomal dysfunction in neurodegeneration: emerging concepts and methods. Trends Neurosci. 45, 184–199. https://doi.org/https://doi.org/10.1016/j.tins.2021.12.004
93. Wang, M., Tang, G., Zhou, C., Guo, H., Hu, Z., Hu, Q., Li, G., 2023. Revisiting the intersection of microglial activation and neuroinflammation in Alzheimer's disease

from the perspective of ferroptosis. Chem. Biol. Interact. 375, 110387. https://doi.org/https://doi.org/10.1016/j.cbi.2023.110387

94. Więckowska-Gacek, A., Mietelska-Porowska, A., Wydrych, M., Wojda, U., 2021. Western diet as a trigger of Alzheimer's disease: From metabolic syndrome and systemic inflammation to neuroinflammation and neurodegeneration. Ageing Res. Rev. 70, 101397. https://doi.org/https://doi.org/10.1016/j.arr.2021.101397
95. Wise, R.M., Wagener, A., Fietzek, U.M., Klopstock, T., Mosharov, E. V, Zucca, F.A., Sulzer, D., Zecca, L., Burbulla, L.F., 2022. Interactions of dopamine, iron, and alpha-synuclein linked to dopaminergic neuron vulnerability in Parkinson's disease and Neurodegeneration with Brain Iron Accumulation disorders. Neurobiol. Dis. 175, 105920. https://doi.org/https://doi.org/10.1016/j.nbd.2022.105920
96. Witkamp, R., 2016. Fatty acids, endocannabinoids and inflammation. Eur. J. Pharmacol. 785, 96–107. https://doi.org/https://doi.org/10.1016/j.ejphar.2015.08.051
97. Yang, Y.-Y., Qi, J.-J., Jiang, S.-Y., Ye, L., 2024. Esculin ameliorates obesity-induced insulin resistance by improving adipose tissue remodeling and activating the IRS1/PI3K/AKT/GLUT4 pathway. J. Ethnopharmacol. 319, 117251. https://doi.org/https://doi.org/10.1016/j.jep.2023.117251
98. Zhang, X., Chen, X., Zhang, L., Sun, Y., Liang, Y., Li, H., Zhang, Y., 2023. Role of trigger receptor 2 expressed on myeloid cells in neuroinflammation—neglected multidimensional regulation of microglia. Neurochem. Int. 171, 105639. https://doi.org/https://doi.org/10.1016/j.neuint.2023.105639
99. Zhou, X., Zhao, R., Lv, M., Xu, X., Liu, W., Li, X., Gao, Y., Zhao, Z., Zhang, Z., Li, Y., Xu, R., Wan, Q., Cui, Y., 2023. ACSL4 promotes microglia-mediated neuroinflammation by regulating lipid metabolism and VGLL4 expression. Brain. Behav. Immun. 109, 331–343. https://doi.org/https://doi.org/10.1016/j.bbi.2023.02.012
100. Zufiría, M., Gil-Bea, F.J., Fernández-Torrón, R., Poza, J.J., Muñoz-Blanco, J.L., Rojas-García, R., Riancho, J., López de Munain, A., 2016. ALS: A bucket of genes, environment, metabolism and unknown ingredients. Prog. Neurobiol. 142, 104–129. https://doi.org/https://doi.org/10.1016/j.pneurobio.2016.05.004
101. Zuo, J., Zhang, T.-H., Peng, C., Xu, B.-J., Dai, O., Lu, Y., Zhou, Q.-M., Xiong, L., 2024. Essential oil from Ligusticum chuanxiong Hort. Alleviates lipopolysaccharide-induced neuroinflammation: Integrating network pharmacology and molecular mechanism evaluation. J. Ethnopharmacol. 319, 117337. https://doi.org/https://doi.org/10.1016/j.jep.2023.117337