**Bulletin of Environment, Pharmacology and Life Sciences**
Bull. Env. Pharmacol. Life Sci., Vol 10 [7] June 2021 : 01-10

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

**REVIEW ARTICLE** **OPEN ACCESS**

# The potential neurobehavioral effects of an anti-asthmatic drug (Montelukast): A Review

**Manjyot Kaur, Anju Sharma**
Department of Zoology, IIS (deemed to be) University, Jaipur, Rajasthan, India.
Email: dranju1110@Gmail.com

**ABSTRACT**

*Montelukast is a leukotriene receptor antagonist, recommended to be used in treatment of asthma and seasonal allergies. This drug has a wide use as it is prescribed to both pediatric and adult patients. Efficacy of any pharmacological treatment is important because drug reaches both pathological target as well as non-target areas in a nonselective manner, thus causing desired but also some unwanted effects. Montelukast has been believed to be safe drug due to mild and transient side effects. However recent studies show that montelukast treatment caused psychiatric adverse effects in children such as sleep disorder, anxiety, aggressiveness and hyperactivity. In present review we focused on the neurobehavioral effect of Montelukast and its neuroprotective potency. It recently emerged role in potential treatment of COVID 19 because of antiviral and anti-fibrosis properties are also discussed.*

***Keywords:*** *Montelukast, adverse drug reaction, leukotriene receptor antagonists, psychiatric disorders, neuroprotection, neurobehavioral, COVID 19.*

Received 04.05.2021 Revised 20.05.2021 Accepted09.06.2021

## INTRODUCTION

Montelukast (ML) is an anti-inflammatory drug used mainly for the treatment of asthma. Itis a leukotriene receptor antagonist (LTRA) that blocks cysteinyl leukotriene type 1 (CysLT1) receptors which are present in human air passage. CysLTs are synthesized by mast cells and basophils via 5-lipoxygenase metabolism of arachidonic acid. CysLTs promote allergic inflammation by increasing the production, adhesion, migration, and survival of inflammatory cells such as eosinophils[1].

Montelukast relieves from allergic and asthmatic symptoms by binding to CysLT1 receptors and blocking the action of leukotriene D4(one of the leukotrienes) on these receptors. The main function of leukotriene is to induce the contraction of smooth muscle which results in bronchoconstriction and vasoconstriction. The binding of montelukast to CysLT1 receptors reduces the bronchoconstriction caused by the leukotriene and lowers the inflammation[2].It is effective in improving clinical parameters of asthmatic inflammation as it possess anti-inflammatory properties[3].Apart from leukotriene receptor antagonists, several other classes of medications for treatment of asthma include inhaled corticosteroids, anticholinergics, beta agonists, zileuton, and newer class monoclonal antibody immune modulating drugs[4].

Montelukast is considered to be a safe drug to treat asthma in both children and adult patients, however recent studies have shown that it causes adverse effects. Most common side effects are vomiting, diarrhea, mild rashes, nausea, fever, and headaches[5]. Adverse events like sleeping disorders and psychiatric disorders have also been reported in some studies[6].While in some animal studies it has improved cognition and exhibited neuroprotective, renoprotective, hepatoprotective effect against certain toxic compounds such as cisplastin, radioactive iodine, cadmium, streptozotocin, methotrexate[7,8,9].This review focuses on both protective and adverse effect of montelukast on mammalian models specifically in relation to brain and behaviour.

## ADVERSE EFFECT OF MONTELUKAST IN HUMANS

Literature review suggested that Montelukast has shown adverse as well as protective effects on various organ system of humans[10-12].During the treatment vomiting, fatigue, nausea and abdominal pain are some of the common adverse effects suspected to be caused by montelukast[11]. Apart from these increased aminotransferase, alkaline phosphatase levels and bilirubin levels were also observed during montelukast treatment. After stopping the treatment with montelukast all the enzyme levels got

normalized[10].It is also reported to cause hepatotoxicity in another study[12].A case of adverse effect was reported in a 46 year old male, in which montelukast was suspected to cause hepatocellular liver injury. The liver test results became normal after suspending montelukast treatment[13]. Cases of severe hypertriglyceridemia development were also observed, which were followed by recovery after discontinuation of montelukast treatment[14].

Another patient gained unusual weight and experienced abdominal pain after 2 months treatment of montelukast. Presence of hypercholesterolemia, acute pancreatitis, and severe hypertriglyceridemia was observed which disappeared after montelukast discontinuation[15]. A 58 year old patient undergoing montelukast treatment started suffering from haematuria, a condition in which there is presence of blood in the urine. After montelukast withdrawal the haematuria improved and later renal function also returned to normal[16].

A case study of a man with moderate asthma who was undergoing montelukast treatment reported development of urticaria, an outbreak of pale red bumps on the skin five days after starting montelukast. The symptoms disappeared after suspension on montelukast treatment[17].Another case of urticaria was reported in a 50 year old woman undergoing montelukast treatment[18]. Severe case of bruising was experienced in a 31 year old woman after starting montelukast treatment[19]. A young women receiving montelukast treatment developed recurrent lip swelling, shortness of breath and skin rash[20].

**PROTECTIVE EFFECTS OF MONTELUKAST IN MAMMALS**

Many recent studies have shown that montelukast has protective effect on various organs including kidney, liver, reproductive organs, pituitary gland, and brain[8,21,22].In a study treatment of montelukast has shown to protect kidneys against damage caused by methotrexate, a cytotoxic chemotherapeutic agent used in treatment of cancers. Methotrexate treatment caused unbalance in tissue oxidative parameters, increased TNF-α levels, and NF-κB expression in renal tissues. Treatment of montelukast normalized kidney specific parameters, oxidative stress, and inflammatory mediators otherwise unbalanced by methotrexate treatment[8]. A recent study has indicated towards hepatoprotective effect of montelukast as its treatment effectively protects the rat liver against damage caused by radioactive iodine treatment. Radioactive iodine is used for diagnosing and treatment of hyperthyroidism and thyroid cancer. Histopathological examination revealed that treatment with radioactive iodine caused presence of inflammatory cells, hyperemia, and capsule thickening in liver tissue. However, treatment of montelukast along with radioactive iodine resulted in less inflammation and thickening in liver[21].

Certain studies also indicated towards anti-inflammatory and anti-oxidant properties of montelukast which protected against oxidative stress caused by various injuries and toxicity[23,24,9]. It has reported to reduce oxidative stress and reproductive toxic effects of cisplatin, a well-known chemotherapeutic drug used to treat a number of cancers. Cisplastin caused oxidative stress, declined the levels of GSH, CAT, GPx, and SOD in rats. Montelukast treatment reversed the effects of cisplatin by an increase in GSH, CAT, GPx, and SOD levels. Cisplastin treatment also resulted in histopathological damage and decreased testosterone level and sperm motility. All these changes were ameliorated by montelukast treatment and thus it was concluded that reproductive toxicity caused by cisplastin may be prevented by ML treatment[7]. In one more study antioxidant, histological, immunohistochemical and hormonal effects of cadmium and montelukast were evaluated. It was found that montelukast restored diminished hormonal level and increased MDA level and depleted oxidative enzymes on pituitary gland of rat exposed to cadmium[9].In another study montelukast has shown protective effect against liver damage in jaundice rat model reported. It was found that animal group receiving montelukast showed significantly less histopathological damage than control group. There was also significant difference between liver myeloperoxidase, malondialdehyde, and total sulfhydryl between montelukast and control group animals[22].

Montelukast is effective in attenuating intestinal ischemia-reperfusion injury. In rats intestinal ischemia resulted in increased CysLTR1 expression in intestine, liver and kidney. Expressions of these receptors were markedly reduced by montelukast treatment[24].Similarly, in another study montelukast has shown protective effect against renal ischemia/reperfusion in rats. Ischemia resulted in decrease in renal glutathione and plasma amine oxidase, accompanied with an increase in malondialdehyde level, myeloperoxidase activity, lactate dehydrogenase activity, creatinine and blood urea nitrogen. However montelukast treatment reversed all these biochemical indices as well as histopathological alterations caused by ischemia, and improved microscopic damage and renal function. It protected kidney tissue by balancing oxidant–antioxidant status, and regulating the generation of inflammatory mediators[23].In another study, montelukast attenuated adverse effects of alendronate, a drug used to treat osteoporosis. Alendronate causes oxidative damage in tissues by increasing myeloperoxidase activity and lipid

peroxidation, and also decreases glutathione level. Montelukast by its anti-inflammatory effect prevented the damage and the changes in biochemical parameters of liver and kidney tissues[25].

**Table 1: Summary of Adverse Effects of Montelukast**

| Reference | Effect observed in | Effect on organ/behavior | Dosage and duration of montelukast treatment | Conclusion |
|---|---|---|---|---|
| Incecik, F., *et al.* [12] | Human patient | Hepatotoxic | 5 mg once a day for 2 years | Montelukast has shown to cause hepatotoxicity. |
| Russmann, S., *et al*. [10] | Human patient | fatigue, vomiting and with elevated aminotransferase, alkaline phosphatase levels and bilirubin | 10 mg once a day for 2 years | Adverse effect of montelukast in a patient were observed characterized by fatigue, vomiting and with elevated aminotransferase, alkaline phosphatase levels and bilirubin. |
| Harugeri, A., *et al.* 2009[13] | Human patient | hepatocellular liver injury | 10 mg once a day | Adverse effect was observed in a 46 year old, in which montelukast was suspected to cause hepatocellular liver injury. |
| Palodhi, S., *et al*.[14] | Human patient | hypertriglyceridemia | 10 mg once a day, for 1 month | Cases of severe hypertriglyceridemia development were also observed in patients, which were followed by recovery after discontinuation of montelukast treatment |
| Das, S., *et al*. [15] | Human patient | hypercholesterolemia, acute pancreatitis, and severe hypertriglyceridemia | 10 mg once a day, for 2 months | Patient gained unusual weight and abdominal pain after 2 months treatment of montelukast. Presence of hypercholesterolemia, acute pancreatitis, and severe hypertriglyceridemia was observed which disappeared after montelukast discontinuation |
| Xie, J., *et al*. [16] | Human patient | Haematuria | | 58 year old patient undergoing montelukast treatment started suffering from haematuria, presence of blood in the urine. After montelukast withdrawal the haematuria improved and later renal function also returned to normal |
| Minciullo, P., *et al*. [17] | Human patient | urticaria | 10 mg once a day, for 5 days | Patient developed urticaria, an outbreak of pale red bumps on the skin five days after starting montelukast. The symptoms disappeared after suspension on montelukast treatment |
| Herzinger, T., *et al*. [18] | Human patient | urticaria | 10 mg once a day, for 3 months | case of urticaria was reported in a 50 year old woman undergoing montelukast treatment |
| Aypak, C., *et al*. 2013[19] | Human patient | bruising | 10 mg once a day, for 1 month | case of bruising was experienced in a 31 year old woman after starting montelukast treatment |
| Tayeb, M., *et al*. [20] | Human patient | lip swelling, shortness of breath and skin rash | 10 mg (single dose) | Women receiving montelukast treatment developed recurrent lip swelling, shortness of breath and skin rash |
| Wallerstedt, S.M., *et .al* [36] | Human patient (children) | Adverse drug reaction | 4mg to 10mg | 48 children patients showed psychiatric disorders including nightmares, unspecified anxiety, aggressiveness, sleep disorders, insomnia, irritability, hallucination, hyperactivity, and personality disorder. |
| Donmez, Y., *et .al* [37] | Human patient | No adverse drug reaction observed | | Short-term (4 to 8 weeks) montelukast use is safe and did not |

| | | | | |
|---|---|---|---|---|
| | (children) | | | cause any psychiatric problems in 30 children |
| Cereza, G., *et al.* [40] | Human patient | Adverse drug reaction | 4mg to 10mg | 24 cases of patient undergoing treatment with montelukast reported nightmares, both in adults and children |
| Byrne, F., *et al*. [38] | Human patient | Adverse drug reaction | 5 mg once a day for 2 years and 6 months | A 9-year-old boy undergoing montelukast therapy for several years experienced neuropsychiatric events consisting of sleepwalking, sleep disturbance, bruxism and anxiety worsened by stressful events. |
| Anandan, N., *et al*. [41] | Human patient | Adverse drug reaction disappeared after stopping montelukast treatment | 10 mg once a day for 48 hour | 29-year-old asthmatic woman experienced auditory and visual hallucinations, which stopped within 2 days after montelukast withdrawal. |
| Alkhuja, S., *et al*. [42] | Human patient | Adverse drug reaction disappeared after stopping montelukast treatment | 10 mg once a day for 24 hour | 16-year-old female who showed daily parasomnias in the form of sleepwalking and sleep talking after taking montelukast and these parasomnias disappeared after discontinuing montelukast. |
| Callero, A., *et al*.[39] | Human patient | Adverse drug reaction disappeared after stopping montelukast treatment | 5 mg once a day for 3 weeks | Four children, aged between 1 and 5 years, developed sleep disorders as well as behavioural and mood disorders while receiving montelukast and after montelukast withdrawal, all these symptoms disappeared. |
| Kocyigit, A., *et al*. [43] | Human patient | Adverse drug reaction disappeared after stopping montelukast treatment | | 13-year-old patient reported visual hallucinations after starting a therapy with montelukast, which disappeared within 48 h after the cessation of drug intake. |

**TABLE 2: SUMMARY OF PROTECTIVE EFFECTS OF MONTELUKAST**

| Reference | Effect observed in | effect on organ/behavior | Dosage and duration of montelukast treatment | Conclusion |
|---|---|---|---|---|
| Abdel-Raheem, I.T., *et al*. [8] | Rats | Renoprotective against methotrexate treatment | 10 mg/kg for 10 days | Montelukast exhibited its renoprotective effect by normalization of kidney specific parameters, oxidative stress, and inflammatory mediators unbalanced by methotrexate treatment |
| Hasan, A., *et al*. [21] | Rats | hepatoprotective against radioactive iodine treatment | 10 mg/kg for 10 days | Montelukast treatment effectively protects the rat liver against damage caused by radioactive iodine treatment especially on hyperemia and capsule thickening. |
| Kuru, S., *et al*. [22] | Rats | protective effect on liver damage in obstructive jaundice | 10 mg/kg | Animal group receiving montelukast showed significantly less histopathological damage than control group. Myeloperoxidase, malondialdehyde, and total sulfhydryl level of liver also differed between montelukast and control group animals. |
| Beytur, A., *et al*. [7] | Rats | protective effect on cisplatin induced reproductive toxicity | 10 mg/kg for 10 days | Montelukast eliminates the effects of cisplatin on sperm motility, serum testosterone level, and on oxidative stress by increasing levels of GSH, CAT, GPx, and SOD levels. |

| | | | | |
|---|---|---|---|---|
| Azeem, E., *et al*. [9] | Rats | Protective against cadmium toxicity on pituitary gland | 10 mg/kg | Montelukast restored diminished hormonal level, increased MDA level and depleted oxidative enzymes on pituitary gland of rat exposed to cadmium. |
| Mansour, R.M., *et al*. [27] | Rats | Neuroprotective effect in rotenone-induced Parkinson's disease model | 10 mg/kg | Montelukast significantly attenuated motor impairment, decreased elevated oxidative stress mediators, declined p53 expression and improved the histopathological changes caused by rotenone. |
| Wu, S., *et al*. [24] | Rats | Montelukast attenuates intestinal ischemia-reperfusion injury | 2 and 20 mg/kg (single dose) | Montelukast reduces the expressions of CysLTR1 receptors which were otherwise increased due to ischemia in intestine, liver and kidney. |
| Yu, G., *et al*. [32] | Mice | Neuroprotective effect on cerebral ischemia in mice | 0.1 and 1.0 mg/kg (single dose) | Intraperitoneal injection of montelukast significantly attenuated all the ischemic insults |
| Sener, G., *et al*. [23] | Rats | renal protective effect against ischemia/ reperfusion | 10 mg/kg (single dose) | Montelukast treatment reversed all the biochemical indices as well as histopathological alterations induced by ischemia, and improved microscopic damage and renal function. It protects kidney tissue by balancing oxidant–antioxidant status, and regulating the generation of inflammatory mediators |
| Sener, G., *et al*. [25] | Rats | Protective effect against adverse effects of Alendronate | 10 mg/kg for 4 days | Montelukast prevented the damage as well as the changes in biochemical parameters in liver and kidney tissues studied, by its anti-inflammatory effect. |
| Marschallinger, J., *et al*. [33] | Rats | Montelukast improves cognition in old rats | 10 mg/kg for 42 days | It was found that montelukast reduces neuroinflammation and increases hippocampal neurogenesis through inhibition of the GPR17 receptor. It also restores learning and improve cognition in old rats. |
| Marschallinger, J., *et al*. [28] | Rats | Montelukast restores memory in animal model of dementia | 10 mg/kg for 42 days | It was found that montelukast reduces alpha-synuclein load and restores memory in an animal model of dementia with lewy bodies. |
| Kumar, A., *et al*. [26] | Rats | Neuroprotective effect of montelukast along with rofecoxib and caffeic acid against kainic acid induced cognitive dysfunction | 0.5 and 1 mg/kg for 14 days | Animal groups receiving treatment with montelukast, rofecoxib and caffeic acid showed improvement in memory performance, oxidative stress parameters and mitochondrial function as compared to that of control animals. |
| Zhang, C., *et al*.[34] | Mice | Protective effect on streptozotocin induced memory deficits | 1 or 2 mg/kg for 3 weeks | Oral treatment of montelukast for 3 weeks remarkably attenuated learning and memory impairments induced by streptozotocin. |
| Abdelzaher, L., *et al.* [35] | Mice | Montelukast alleviates autistic behavior induced by thimerosal treatment | 10 mg/kg for 3 weeks | Intraperitonial montelukast administration ameliorated thimerosal induced social deficit and inflammation. |

**Neuroprotective role of montelukast:**

Montelukast has shown neuroprotective activity in various animal studies[26-28]. It is a leukotriene receptor antagonist which binds to the CysLT1 and CysLT2 receptors, which are expressed in different brain regions namely hypothalamus, thalamus, putamen, pituitary, and medulla[29]. Increased levels of

leukotrienes in brain contribute to acute and chronic lesions[30]and in aged brain it may mediate neuroinflammatory responses including microglia activation[31].

Neuroprotective effect of montelukast was elucidated in a study on rotenone-induced Parkinson's disease rat model. Rotenone, a broad-spectrum insecticide treatment caused reduction in motor functioning and elevated oxidative stress markers. However, treatment with montelukast attenuated motor impairment, decreased the rise in oxidative stress mediators, declined p53 expression and showed improvement in the histopathological changes incited by rotenone[27].

In another study dose and time dependent neuroprotective effect of montelukast on cerebral ischemia in mice was observed. Intraperitoneal injection of montelukast one hour before the cerebral ischemia attenuated all the ischemic insults. However, post-treatment of montelukast (1 hour after cerebral ischemia) had no significant effect. Thus, these findings indicate toward therapeutic potential of montelukast in the treatment of cerebral ischemia at earlier phases[32].

In a study conducted on young (4 months) and old (20 months) rats it was found that montelukast reduces neuroinflammation and increases hippocampal neurogenesis through inhibition of the GPR17 receptor. It also restores learning and improves cognition in old rats. But no effect on cognition of young rat and on general behavior of both young and old rat was observed. This works findings concluded that montelukast might be a safe drug to restore cognitive functions in old individuals and for the treatment of dementias[33].

In a different study on a mice model of dementia with lewy bodies, it was found that treatment of montelukast reduces alpha-synuclein load and restores memory in mice. It was observed that cognitively deficient transgenic mice (expressing human wild-type alpha-synuclein) receiving 6-week treatment with montelukast showed increased tendency for learning compared to the control groups. Montelukast treatment caused modulation of beclin-1 expression which is a marker for autophagy, and in a reduction in the human alpha-synulcein load in the transgenic mice. This work suggests that montelukast by reducing the protein aggregation might be helpful in treating neurodegenerative diseases and dementia[28].

Neuroprotective effect of montelukast treatment along with rofecoxib and caffeic acid was evaluated against kainic acid. Kainic acid is a potent neuroexcitatory amino acid agonist, whose treatment induced cognitive dysfunction in rats. Significant improvement in memory performance, oxidative stress parameters and mitochondrial function was observed in animals receiving treatment with montelukast, rofecoxib and caffeic acid as compared to that of control animals[26].

Beneficial effect of montelukast on streptozotocin induced memory deficits in mice was also investigated. Streptozotocin is a toxic agent to beta cells of the pancreas in mammals. Intra-hippocampal microinfusion of streptozotocin caused learning and memory impairments, caused neuroinflammatory and apoptotic responses in hippocampus and up-regulated protein and mRNA of CysLT1R in hippocampus. Oral treatment of montelukast attenuated harmful effects induced by streptozotocin. Results of this study suggest that montelukast improves memory impairment and inhibits neuroinflammation and apoptosis in mice exposed and thus montelukast may provide a novel strategy for treating or preventing Alzheimer's disease[34].

In a recent study it was observed that montelukast is also useful in alleviating autistic behavior induced by thimerosal treatment in mice. Treatment of thimerosal, a mercury-containing organic compound impaired social activity and growth development in mice. However intraperitoneal montelukast administration ameliorated thimerosal induced social deficit. It also suppressed thimerosal induced toxicity and inflammation[35].

**Behavioral effects of montelukast:**

Number of human studies has reported behavioral changes during treatment with montelukast. In a study conducted on children receiving montelukast treatment, behavioural changes related to psychiatric disorders like nightmares, unspecified anxiety, aggressiveness, sleep disorders, insomnia, irritability, hallucination, hyperactivity and personality disorder were observed. In 80% of these reported cases, the duration from exposure to experiencing of adverse drug reaction was less than 1 week[36]. However, in a different study conducted on 30 children it was found that short-term (4 to 8 weeks) montelukast use is safe and do not cause any psychiatric problems in children[37].According to another data collected in Sweden during 1998-2007, it was indicated that out of 48 psychiatric adverse drug reaction induced due to montelukast, the most common were nightmares and hallucinations.

Apart from previously described psychiatric problems several cases of other adverse drug reactions have been reported like sleep disturbances and nightmares[38-40].Twenty four patient including adults and children, undergoing montelukast treatment reported nightmares[40].A 9-year-old boy undergoing montelukast therapy for several years experienced neuropsychiatric events consisting of sleepwalking, sleep disturbance, bruxism and anxiety worsened by stressful events[38].

Several cases have been reported in which adverse psychiatric effects disappeared after stopping montelukast treatment[41-43].An adult asthmatic woman reported auditory and visual hallucinations, which stopped within 2 days after montelukast withdrawal[41]. In another case, a child patient experienced visual hallucinations after starting a therapy with montelukast, which disappeared within 48 h after the cessation of drug intake[43].A female child showed daily parasomnias in the form of sleepwalking and sleep talking after taking montelukast and these parasomnias disappeared after discontinuing montelukast[25]. In another case it was observed that four children, aged between 1 and 5 years, developed sleep disorders (i.e. insomnia, somnolence and night terrors) as well as behavioural and mood disorders while receiving montelukast and after montelukast withdrawal, all these symptoms disappeared[39].

In previously discussed articles, both adults and children seem to develop psychiatric symptoms such as hallucinations, sleep walking, nightmares, anxiety, depression, aggression and headaches after the intake of the medication and symptoms becomes less after discontinuation of the therapy with montelukast.

**Montelukast as a potential treatment of COVID 19:**

Apart from previously discussed protective effects of montelukast, it has now emerged as a potential treatment of COVID 19. Studies have suggested that montelukast has improved COVID 19 prognosis as it possesses antiviral, anti-fibrosis properties and is protective against neuropsychiatric disorders[44-47].

Montelukast has shown antiviral properties against certain viral disease. It was found that montelukast inhibited Influenzae A virus gene expression by PERK phosphorylation. However, it did not alter viral RNA synthesis *in vitro* or viral RNA accumulation *in vivo*[44].In a study role of montelukast was investigated against hepatitis C virus. This study concluded that treatment of montelukast decreased the level of RNAs expressed by inhibiting viral replication[48]. In another study beneficiary action of montelukast against Zika virus was also reported. Montelukast treatment has been beneficial as it possesses antiviral properties and can antagonize cytokine storm[45].

In a study conducted on mice it was found that montelukast is also protective against respiratory syncytial virus. Viral infection induced cysLT release, which was decreased by montelukast treatment and it also attenuated viral induced inflammation and IFN-γ production in infected adult and neonate mice[49].

Many COVID 19 patients have been reported to experience central nervous system disorders involving headache, stroke, seizures and anosmia[47].On the other hand montelukast has shown neuroprotective effects in many animal studies. It been reported to improve recovery after brain ischemia, enhancing recruitment and maturation of oligodendrocyte precursor cells[50]. Additionally six week treatment of montelukast reduced neuroinflammation and elevated hippocampal neurogenesis through inhibition of the GPR17 receptor in younger and older rats with potential benefits for the prevention of manifestations such as delirium[33].

COVID-19 is also associated with increased risk of cytokine storm i.e., generation of both pro-inflammatory and anti-inflammatory cytokines by the innate immune system[51].Montelukast treatment causes decrease frequency and intensity of cytokine reactions[52]. Also, clinically, montelukast is used to reduce drug-related cytokine reactions induced by rituximab[52]and daratumumab[53].

COVID-19 may also result in pulmonary firbrosis or scar formation in lungs[54]. Montelukast is also known to possess anti fibrosis properties as it regulates the extracellular remodeling matrix and inhibits the formation of fibrosis. In a study protective effect of montelukast was investigated in bleomycin-induced pulmonary fibrosis[55]. In another study it was found that montelukast treatment attenuates bleomycin-induced inflammatory and oxidative lung injury and prevents lung fibrotic response[56].

As montelukast possess anti-inflammatory effects, suppress oxidative stress and reduce affect cytokine production, so it has been hypothesized that its treatment may limit progression of the disease on COVID-19 infection[46].

## CONCLUSION

In this review we highlighted that apart from being a commonly used drug for asthma treatment, montelukast also has neuroprotective potency. This review also focuses on therapeutic effectiveness of montelukast in COVID 19 treatment.

## CONFLICT OF INTEREST

There is no conflict of interest.

## REFERENCES

1. Peters-Golden, M., Gleason, M.M., & Togias, A. (2006). Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. Clin. Exp. Allergy., 36(6):689–703.

2. Zubairi, A.B., Salahuddin, N., Khawaja, A., Awan, S., Shah, A.A., Haque, A. S., Husain, S.J., Rao, N., & Khan, J.A. (2013). A randomized, double-blind, placebo-controlled trial of oral montelukast in acute asthma exacerbation. BMC. Pulm. Med., 13:20.
3. Shirasaki, H., Kanaizumi, E., Seki, N., Fujita, M., Kikuchi. M., Himi. T. (2013). Localization and up-regulation of cysteinyl leukotriene-2 receptor in human allergic nasal mucosa. Allergol. Int., 62(2):223-228.
4. Bush, A. (2018). Management of asthma in children. Minerva. Pediatr., 70(5):444-457.
5. Haarman, M.G., van Hunsel, F., & de Vries, T.W. (2017). Adverse drug reactions of montelukast in children and adults. Pharmacol. Res. Perspect., 5(5):e00341.
6. Calapai, G., Casciaro, M., Miroddi, M., Calapai, F., Navarra, M., & Gangemi, S. (2014). Montelukast-induced adverse drug reactions: a review of case reports in the literature. Pharmacology., 94(1-2):60–70.
7. Beytur, A., Ciftci, O., Oguz, F., Oguzturk, H., & Yilmaz, F. (2012). Montelukast attenuates side effects of cisplatin including testicular, spermatological, and hormonal damage in male rats. Cancer. Chemother. Pharmacol., 69(1):207–213.
8. Abdel-Raheem, I.T., & Khedr, N.F. (2014). Renoprotective effects of montelukast, a cysteinyl leukotriene receptor antagonist, against methotrexate-induced kidney damage in rats. Naunyn. Schmiedebergs. Arch. Pharmacol., 387(4):341–353.
9. Abd-El-Azeem, E.K., Abass, M.F., Paulis, M.G., Nisreen, Abd-eltawab, Abd-Elgaber. (2017). Protective Effect of Montelukast against Cadmium Induced Pituitary Gland Toxicity. Int. J. Clin. Pharmacol. Toxicol., 6(2):256-261.
10. Russmann, S., Iselin, H.U., Meier, D., Zimmermann, A., Simon, H.U., Caduff, P., & Reichen, J. (2003). Acute hepatitis associated with montelukast. J. Hepatol., 38(5):694–695.
11. Actis, G.C., Bugianesi, E., Ottobrelli, A., & Rizzetto, M. (2007). Fatal liver failure following food supplements during chronic treatment with montelukast. Dig. Liver. Dis., 39(10):953–955.
12. Incecik, F., Onlen, Y., Sangun, O., & Akoglu, S. (2007). Probable montelukast-induced hepatotoxicity in a pediatric patient: case report. Ann. Saudi. Med., 27(6):462–463.
13. Harugeri, A., Parthasarathi, G., Sharma, J., D'Souza, G. A., & Ramesh, M. (2009). Montelukast induced acute hepatocellular liver injury. J. Postgrad. Med., 55(2):141–142.
14. Palodhi, S., Ray-Chaudhuri, P., Biswas, A., & Bera, T. (2012). Montelukast induced hypertriglyceridemia. Indian. Med. Gaz.,145(8):334-336.
15. Das, S., Mondal, S., Dey, J.K., Bandyopadhyay, S., Saha, I., & Tripathi, S.K. (2013). A case of montelukast induced hypercholesterolemia, severe hypertriglyceridemia and pancreatitis. J. Young. Pharm., 5(2):64–66.
16. Xie, J.X., Wei, J.F., & Meng, L. (2013). Montelukast sodium-induced hematuria: a case report and literature review of 19 cases in mainland China. Int. J. Clin. Pharmacol. Ther., 51(12):958–962.
17. Minciullo, P.L., Saija, A., Bonanno, D., Ferlazzo, E., & Gangemi, S. (2004). Montelukast-induced generalized urticaria. Ann. Pharmacother., 38(6):999–1001.
18. Herzinger, T., Ludolph-Hauser, D., & Przybilla, B. (2008). Urticaria triggered by antiallergy treatment. Clin. Exp. Dermatol., 33(4):519–520.
19. Aypak, C., Türedi, Ö., Solmaz, N., Yıkılkan, H., & Görpelioğlu, S. (2013). A rare adverse effect of montelukast treatment: ecchymosis. Respir. Care., 58(9):e104–e106.
20. Tayeb, MMS. (2013). Allergy to Montelukast Sodium Treated Effectively by Protracted Oral Desensitization: First Case Report. J. Aller. Ther., 4(1):129-133.
21. Atilgan, H.I., Yumusak, N., Sadic, M., Gultekin, S.S, Koca, G., Ozyurt, S., Demirel, K., & Korkmaz, M. (2015). Radioprotective effect of montelukast sodium against hepatic radioiodine (I-131) toxicity: A histopathological investigation in the rat model. Ankara. Üniv. Vet. Fak. Derg., 62(1):37-43.
22. Kuru, S., Kismet, K., Barlas, A. M., Tuncal, S., Celepli, P., Surer, H., Ogus, E., & Ertas, E. (2015). The Effect of Montelukast on Liver Damage in an Experimental Obstructive Jaundice Model. Viszeralmedizin., 31(2):131–138.
23. Sener, G., Sehirli, O., Velioğlu-Oğünç, A., Cetinel, S., Gedik, N., Caner, M., Sakarcan, A., & Yeğen, B.C. (2006). Montelukast protects against renal ischemia/reperfusion injury in rats. Pharmacol. Res., 54(1):65–71.
24. Wu, S., Zhu, X., Jin, Z., Tong, X., Zhu, L., Hong, X., Zhu, X., Liu, P., & Shen, W. (2015). The protective role of montelukast against intestinal ischemia-reperfusion injury in rats. Sci. Rep., 5:15787.
25. Sener, G., Kapucu, C., Cetinel, S., Cikler, E., & Ayanoğlu-Dülger, G. (2005). Gastroprotective effect of leukotriene receptor blocker montelukast in alendronat-induced lesions of the rat gastric mucosa. Prostaglandins. Leukot. Essent. Fatty. Acids., 72(1):1–11.
26. Kumar, A., Prakash, A., Pahwa, D., & Mishra, J. (2012). Montelukast potentiates the protective effect of rofecoxib against kainic acid-induced cognitive dysfunction in rats. Pharmacol. Biochem. Behav., 103(1):43–52.
27. Mansour, R.M., Ahmed, M., El-Sahar, A.E., & El Sayed, N.S. (2018). Montelukast attenuates rotenone-induced microglial activation/p38 MAPK expression in rats: Possible role of its antioxidant, anti-inflammatory and antiapoptotic effects. Toxicol. Appl. Pharmacol., 358:76–85.
28. Marschallinger, J., Altendorfer, B., Rockenstein, E., Holztrattner, M., Garnweidner-Raith, J., Pillichshammer, N., Leister, I., Hutter-Paier, B., Strempfl, K., Unger, M.S., Chishty, M., Felder, T., Johnson, M., Attems, J., Masliah, E., & Aigner, L. (2020). The Leukotriene Receptor Antagonist Montelukast Reduces Alpha-Synuclein Load and Restores Memory in an Animal Model of Dementia with Lewy Bodies. Neurotherapeutics., 17(3):1061–1074.
29. Heise, C.E., O'Dowd, B.F., Figueroa, D.J., Sawyer, N., Nguyen, T., Im, D.S., Stocco, R., Bellefeuille, J.N., Abramovitz, M., Cheng, R., Williams, D.L., Jr, Zeng, Z., Liu, Q., Ma, L., Clements, M.K., Coulombe, N., Liu, Y., Austin, C.P., George, S.R., O'Neill, G.P., Evans, J.F. (2000). Characterization of the human cysteinyl leukotriene 2 receptor. J. Biol. Chem., 275(39):30531–30536.

30. Hu, H., Chen, G., Zhang, J.M., Zhang, W.P., Zhang, L., Ge, Q.F., Yao, H.T., Ding, W., Chen, Z., & Wei, E.Q. (2005). Distribution of cysteinyl leukotriene receptor 2 in human traumatic brain injury and brain tumors. Acta. Pharmacol. Sin., 26(6):685–690.
31. Zhang, W.P., Hu, H., Zhang, L., Ding, W., Yao, H.T., Chen, K.D., Sheng, W.W., Chen, Z., & Wei, E.Q. (2004). Expression of cysteinyl leukotriene receptor 1 in human traumatic brain injury and brain tumors. Neurosci. Lett., 363(3):247–251.
32. Yu, G.L., Wei, E.Q., Zhang, S.H., Xu, H.M., Chu, L.S., Zhang, W.P., Zhang, Q., Chen, Z., Mei, R.H., & Zhao, M.H. (2005). Montelukast, a cysteinyl leukotriene receptor-1 antagonist, dose- and time-dependently protects against focal cerebral ischemia in mice. Pharmacology., 73(1):31–40.
33. Marschallinger, J., Schäffner, I., Klein, B., Gelfert, R., Rivera, F.J., Illes, S., Grassner, L., Janssen, M., Rotheneichner, P., Schmuckermair, C., Coras, R., Boccazzi, M., Chishty, M., Lagler, F. B., Renic, M., Bauer, H. C., Singewald, N., Blümcke, I., Bogdahn, U., Couillard-Despres, S., Aigner, L. (2015). Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat. Commun., 6:8466.
34. Zhang, C.T., Lin, J.R., Wu, F., Ghosh, A., Tang, S. S., Hu, M., Long, Y., Sun, H.B., & Hong, H. (2016). Montelukast ameliorates streptozotocin-induced cognitive impairment and neurotoxicity in mice. Neurotoxicology., 57:214–222.
35. Abdelzaher, L.A., Hussein, O.A., & Ashry, I. (2021). The Novel Potential Therapeutic Utility of Montelukast in Alleviating Autistic Behavior Induced by Early Postnatal Administration of Thimerosal in Mice. Cell. Mol. Neurobiol., 41(1):129–150.
36. Wallerstedt, S.M., Brunlöf, G., Sundström, A., & Eriksson, A.L. (2009). Montelukast and psychiatric disorders in children. Pharmacoepidemiol. Drug. Saf., 18(9):858–864.
37. Donmez, Y.E, & Karaer, I.C. (2020). Does short-term montelukast treatment cause sleep problems or psychiatric problems in children? A preliminary study. Ann. Med. Res., 27(10):2654-2660.
38. Byrne, F., Oluwole, B., Whyte, V., Fahy, S., & McGuinness, D. (2012). Delayed Onset of Neuropsychiatric Effects Associated with Montelukast. Ir. J. Psychol. Med., 29(2):125–127.
39. Callero-Viera, A., Infante, S., Fuentes-Aparicio, V., Zapatero, L., & Alonso-Lebrero, E. (2012). Neuropsychiatric reactions to montelukast. J. Investig. Allergol. Clin. Immunol., 22(6):452–453.
40. Cereza, G., Garcia Doladé, N., & Laporte, J. R. (2012). Nightmares induced by montelukast in children and adults. Eur. Respir J., 40(6):1574–1575.
41. Anandan, N., & Ibitoye, F. (2008). Montelukast and worsening of hallucinations in paranoid schizophrenia. Psychol. Bull., 32(7):276.
42. Alkhuja, S., Gazizov, N., & Alexander, M.E. (2013). Sleeptalking! Sleepwalking! Side effects of montelukast. Case. Rep. Pulmonol., 2013;813786.
43. Kocyigit, A., Gulcan Oksuz, B., Yarar, F., Uzun, F., Igde, M., & Islek, I. (2013). Hallucination development with montelukast in a child with asthma: case presentation. Iran. J. Allergy. Asthma. Immunol., 12(4):397–399.
44. Landeras-Bueno, S., Fernández, Y., Falcón, A., Oliveros, J.C., & Ortín, J. (2016). Chemical Genomics Identifies the PERK-Mediated Unfolded Protein Stress Response as a Cellular Target for Influenza Virus Inhibition. mBio., 7(2):e00085–e16.
45. Chen, Y., Li, Y., Wang, X., & Zou, P. (2020). Montelukast, an Anti-asthmatic Drug, Inhibits Zika Virus Infection by Disrupting Viral Integrity. Frontiers in microbiology, 10:3079.
46. Fidan, C., & Aydoğdu, A. (2020). As a potential treatment of COVID-19: Montelukast. Med Hypotheses., 142:109828.
47. Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA. Neurol., 77(6):683–690.
48. Ruiz, I., Nevers, Q., Hernández, E., Ahnou, N., Brillet, R., Softic, L., Donati, F., Berry, F., Hamadat, S., Fourati, S., Pawlotsky, J. M., & Ahmed-Belkacem, A. (2020). MK-571, a Cysteinyl Leukotriene Receptor 1 Antagonist, Inhibits Hepatitis C Virus Replication. Antimicrob. Agents. Chemother., 64(6):e02078-19.
49. Han, J., Jia, Y., Takeda, K., Shiraishi, Y., Okamoto, M., Dakhama, A., & Gelfand, E. W. (2010). Montelukast during primary infection prevents airway hyperresponsiveness and inflammation after reinfection with respiratory syncytial virus. Am. J. Respir. Crit. Car Med., 182(4):455–463.
50. Gelosa, P., Bonfanti, E., Castiglioni, L., Delgado-Garcia, J. M., Gruart, A., Fontana, L., Gotti, M., Tremoli, E., Lecca, D., Fumagalli, M., Cimino, M., Aigner, L., Abbracchio, M. P., & Sironi, L. (2019). Improvement of fiber connectivity and functional recovery after stroke by montelukast, an available and safe anti-asthmatic drug. Pharmacol. Res., 142:223–236.
51. Russell, B., Moss, C., George, G., Santaolalla, A., Cope, A., Papa, S., & Van Hemelrijck, M. (2020). Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience., 14:1022.
52. Kotchetkov, R., McLean, J., Nay, D., Gerard, L., Hopkins, S., & Didiodato, G. (2020). Premedication with montelukast and rupatadine decreased rituximab infusion time, rate, severity of reactions and use of rescue medications. Int. J. Can., 147(7):1979–1986.
53. Chari, A., Lonial, S., Mark, T. M., Krishnan, A. Y., Stockerl-Goldstein, K. E., Usmani, S. Z., Londhe, A., Etheredge, D., Fleming, S., Liu, B., Ukropec, J., Lin, T. S., Jagannath, S., & Nooka, A. K. (2018). Results of an early access treatment protocol of daratumumab in United States patients with relapsed or refractory multiple myeloma. Cancer., 124(22):4342–4349.

54. Peng, J., Zhou, H., Kuang, G., Xie, L., Tian, T., & Liu, R. (2017). The selective cysteinyl leukotriene receptor 1 (CysLT1R) antagonist montelukast regulates extracellular matrix remodeling. Biochem. Biophys. Res. Commun., 484(3):474–479.
55. Debelleix, S., Siao-Him Fa, V., Begueret, H., Berger, P., Kamaev, A., Ousova, O., Marthan, R., & Fayon, M. (2018). Montelukast reverses airway remodeling in actively sensitized young mice. Pediatr. Pulmonol., 53(6):701–709
56. Topaloğlu, N., Olgun Yıldızeli, Ş., Şener, G., Laçin, T., Şehirli, Ö., Bozkurtlar, E., Çelikel, Ç., & Ceyhan, B. (2018). Protective effect of cysteinyl leukotriene receptor antagonist montelukast in bleomycin-induced pulmonary fibrosis. Turk. Gogus. Kalp. Damar. Cerrahisi. Derg., 26(4):588–597.

**CITATION OF THIS ARTICLE**

Kaur M, & Sharma A. The potential neurobehavioral effects of an anti-asthmatic drug (Montelukast): A Review. Bull. Env. Pharmacol. Life Sci., Vol10[7] June 2021 :01-10

**Bulletin of Environment, Pharmacology and Life Sciences**
Bull. Env. Pharmacol. Life Sci., Vol 10 [7] June 2021 : 01-10

Online ISSN 2277-1808
Journal's URL:http://www.bepls.com
CODEN: BEPLAD

**REVIEW ARTICLE** **OPEN ACCESS**

# The potential neurobehavioral effects of an anti-asthmatic drug (Montelukast): A Review

**Manjyot Kaur, Anju Sharma**
Department of Zoology, IIS (deemed to be) University, Jaipur, Rajasthan, India.
Email: dranju1110@Gmail.com

**ABSTRACT**

*Montelukast is a leukotriene receptor antagonist, recommended to be used in treatment of asthma and seasonal allergies. This drug has a wide use as it is prescribed to both pediatric and adult patients. Efficacy of any pharmacological treatment is important because drug reaches both pathological target as well as non-target areas in a nonselective manner, thus causing desired but also some unwanted effects. Montelukast has been believed to be safe drug due to mild and transient side effects. However recent studies show that montelukast treatment caused psychiatric adverse effects in children such as sleep disorder, anxiety, aggressiveness and hyperactivity. In present review we focused on the neurobehavioral effect of Montelukast and its neuroprotective potency. It recently emerged role in potential treatment of COVID 19 because of antiviral and anti-fibrosis properties are also discussed.*

***Keywords:*** *Montelukast, adverse drug reaction, leukotriene receptor antagonists, psychiatric disorders, neuroprotection, neurobehavioral, COVID 19.*

Received 04.05.2021 Revised 20.05.2021 Accepted09.06.2021

## INTRODUCTION

Montelukast (ML) is an anti-inflammatory drug used mainly for the treatment of asthma. Itis a leukotriene receptor antagonist (LTRA) that blocks cysteinyl leukotriene type 1 (CysLT1) receptors which are present in human air passage. CysLTs are synthesized by mast cells and basophils via 5-lipoxygenase metabolism of arachidonic acid. CysLTs promote allergic inflammation by increasing the production, adhesion, migration, and survival of inflammatory cells such as eosinophils[1].

Montelukast relieves from allergic and asthmatic symptoms by binding to CysLT1 receptors and blocking the action of leukotriene D4(one of the leukotrienes) on these receptors. The main function of leukotriene is to induce the contraction of smooth muscle which results in bronchoconstriction and vasoconstriction. The binding of montelukast to CysLT1 receptors reduces the bronchoconstriction caused by the leukotriene and lowers the inflammation[2].It is effective in improving clinical parameters of asthmatic inflammation as it possess anti-inflammatory properties[3].Apart from leukotriene receptor antagonists, several other classes of medications for treatment of asthma include inhaled corticosteroids, anticholinergics, beta agonists, zileuton, and newer class monoclonal antibody immune modulating drugs[4].

Montelukast is considered to be a safe drug to treat asthma in both children and adult patients, however recent studies have shown that it causes adverse effects. Most common side effects are vomiting, diarrhea, mild rashes, nausea, fever, and headaches[5]. Adverse events like sleeping disorders and psychiatric disorders have also been reported in some studies[6].While in some animal studies it has improved cognition and exhibited neuroprotective, renoprotective, hepatoprotective effect against certain toxic compounds such as cisplastin, radioactive iodine, cadmium, streptozotocin, methotrexate[7,8,9].This review focuses on both protective and adverse effect of montelukast on mammalian models specifically in relation to brain and behaviour.

## ADVERSE EFFECT OF MONTELUKAST IN HUMANS

Literature review suggested that Montelukast has shown adverse as well as protective effects on various organ system of humans[10-12].During the treatment vomiting, fatigue, nausea and abdominal pain are some of the common adverse effects suspected to be caused by montelukast[11]. Apart from these increased aminotransferase, alkaline phosphatase levels and bilirubin levels were also observed during montelukast treatment. After stopping the treatment with montelukast all the enzyme levels got

normalized[10].It is also reported to cause hepatotoxicity in another study[12].A case of adverse effect was reported in a 46 year old male, in which montelukast was suspected to cause hepatocellular liver injury. The liver test results became normal after suspending montelukast treatment[13]. Cases of severe hypertriglyceridemia development were also observed, which were followed by recovery after discontinuation of montelukast treatment[14].

Another patient gained unusual weight and experienced abdominal pain after 2 months treatment of montelukast. Presence of hypercholesterolemia, acute pancreatitis, and severe hypertriglyceridemia was observed which disappeared after montelukast discontinuation[15]. A 58 year old patient undergoing montelukast treatment started suffering from haematuria, a condition in which there is presence of blood in the urine. After montelukast withdrawal the haematuria improved and later renal function also returned to normal[16].

A case study of a man with moderate asthma who was undergoing montelukast treatment reported development of urticaria, an outbreak of pale red bumps on the skin five days after starting montelukast. The symptoms disappeared after suspension on montelukast treatment[17].Another case of urticaria was reported in a 50 year old woman undergoing montelukast treatment[18]. Severe case of bruising was experienced in a 31 year old woman after starting montelukast treatment[19]. A young women receiving montelukast treatment developed recurrent lip swelling, shortness of breath and skin rash[20].

**PROTECTIVE EFFECTS OF MONTELUKAST IN MAMMALS**

Many recent studies have shown that montelukast has protective effect on various organs including kidney, liver, reproductive organs, pituitary gland, and brain[8,21,22].In a study treatment of montelukast has shown to protect kidneys against damage caused by methotrexate, a cytotoxic chemotherapeutic agent used in treatment of cancers. Methotrexate treatment caused unbalance in tissue oxidative parameters, increased TNF-α levels, and NF-κB expression in renal tissues. Treatment of montelukast normalized kidney specific parameters, oxidative stress, and inflammatory mediators otherwise unbalanced by methotrexate treatment[8]. A recent study has indicated towards hepatoprotective effect of montelukast as its treatment effectively protects the rat liver against damage caused by radioactive iodine treatment. Radioactive iodine is used for diagnosing and treatment of hyperthyroidism and thyroid cancer. Histopathological examination revealed that treatment with radioactive iodine caused presence of inflammatory cells, hyperemia, and capsule thickening in liver tissue. However, treatment of montelukast along with radioactive iodine resulted in less inflammation and thickening in liver[21].

Certain studies also indicated towards anti-inflammatory and anti-oxidant properties of montelukast which protected against oxidative stress caused by various injuries and toxicity[23,24,9]. It has reported to reduce oxidative stress and reproductive toxic effects of cisplatin, a well-known chemotherapeutic drug used to treat a number of cancers. Cisplastin caused oxidative stress, declined the levels of GSH, CAT, GPx, and SOD in rats. Montelukast treatment reversed the effects of cisplatin by an increase in GSH, CAT, GPx, and SOD levels. Cisplastin treatment also resulted in histopathological damage and decreased testosterone level and sperm motility. All these changes were ameliorated by montelukast treatment and thus it was concluded that reproductive toxicity caused by cisplastin may be prevented by ML treatment[7]. In one more study antioxidant, histological, immunohistochemical and hormonal effects of cadmium and montelukast were evaluated. It was found that montelukast restored diminished hormonal level and increased MDA level and depleted oxidative enzymes on pituitary gland of rat exposed to cadmium[9].In another study montelukast has shown protective effect against liver damage in jaundice rat model reported. It was found that animal group receiving montelukast showed significantly less histopathological damage than control group. There was also significant difference between liver myeloperoxidase, malondialdehyde, and total sulfhydryl between montelukast and control group animals[22].

Montelukast is effective in attenuating intestinal ischemia-reperfusion injury. In rats intestinal ischemia resulted in increased CysLTR1 expression in intestine, liver and kidney. Expressions of these receptors were markedly reduced by montelukast treatment[24].Similarly, in another study montelukast has shown protective effect against renal ischemia/reperfusion in rats. Ischemia resulted in decrease in renal glutathione and plasma amine oxidase, accompanied with an increase in malondialdehyde level, myeloperoxidase activity, lactate dehydrogenase activity, creatinine and blood urea nitrogen. However montelukast treatment reversed all these biochemical indices as well as histopathological alterations caused by ischemia, and improved microscopic damage and renal function. It protected kidney tissue by balancing oxidant–antioxidant status, and regulating the generation of inflammatory mediators[23].In another study, montelukast attenuated adverse effects of alendronate, a drug used to treat osteoporosis. Alendronate causes oxidative damage in tissues by increasing myeloperoxidase activity and lipid

peroxidation, and also decreases glutathione level. Montelukast by its anti-inflammatory effect prevented the damage and the changes in biochemical parameters of liver and kidney tissues[25].

**Table 1: Summary of Adverse Effects of Montelukast**

| Reference | Effect observed in | Effect on organ/behavior | Dosage and duration of montelukast treatment | Conclusion |
|---|---|---|---|---|
| Incecik, F., *et al.* [12] | Human patient | Hepatotoxic | 5 mg once a day for 2 years | Montelukast has shown to cause hepatotoxicity. |
| Russmann, S., *et al*. [10] | Human patient | fatigue, vomiting and with elevated aminotransferase, alkaline phosphatase levels and bilirubin | 10 mg once a day for 2 years | Adverse effect of montelukast in a patient were observed characterized by fatigue, vomiting and with elevated aminotransferase, alkaline phosphatase levels and bilirubin. |
| Harugeri, A., *et al.* 2009[13] | Human patient | hepatocellular liver injury | 10 mg once a day | Adverse effect was observed in a 46 year old, in which montelukast was suspected to cause hepatocellular liver injury. |
| Palodhi, S., *et al*.[14] | Human patient | hypertriglyceridemia | 10 mg once a day, for 1 month | Cases of severe hypertriglyceridemia development were also observed in patients, which were followed by recovery after discontinuation of montelukast treatment |
| Das, S., *et al*. [15] | Human patient | hypercholesterolemia, acute pancreatitis, and severe hypertriglyceridemia | 10 mg once a day, for 2 months | Patient gained unusual weight and abdominal pain after 2 months treatment of montelukast. Presence of hypercholesterolemia, acute pancreatitis, and severe hypertriglyceridemia was observed which disappeared after montelukast discontinuation |
| Xie, J., *et al*. [16] | Human patient | Haematuria | | 58 year old patient undergoing montelukast treatment started suffering from haematuria, presence of blood in the urine. After montelukast withdrawal the haematuria improved and later renal function also returned to normal |
| Minciullo, P., *et al*. [17] | Human patient | urticaria | 10 mg once a day, for 5 days | Patient developed urticaria, an outbreak of pale red bumps on the skin five days after starting montelukast. The symptoms disappeared after suspension on montelukast treatment |
| Herzinger, T., *et al*. [18] | Human patient | urticaria | 10 mg once a day, for 3 months | case of urticaria was reported in a 50 year old woman undergoing montelukast treatment |
| Aypak, C., *et al*. 2013[19] | Human patient | bruising | 10 mg once a day, for 1 month | case of bruising was experienced in a 31 year old woman after starting montelukast treatment |
| Tayeb, M., *et al*. [20] | Human patient | lip swelling, shortness of breath and skin rash | 10 mg (single dose) | Women receiving montelukast treatment developed recurrent lip swelling, shortness of breath and skin rash |
| Wallerstedt, S.M., *et .al* [36] | Human patient (children) | Adverse drug reaction | 4mg to 10mg | 48 children patients showed psychiatric disorders including nightmares, unspecified anxiety, aggressiveness, sleep disorders, insomnia, irritability, hallucination, hyperactivity, and personality disorder. |
| Donmez, Y., *et .al* [37] | Human patient | No adverse drug reaction observed | | Short-term (4 to 8 weeks) montelukast use is safe and did not |

| | | | | |
|---|---|---|---|---|
| | (children) | | | cause any psychiatric problems in 30 children |
| Cereza, G., *et al.* [40] | Human patient | Adverse drug reaction | 4mg to 10mg | 24 cases of patient undergoing treatment with montelukast reported nightmares, both in adults and children |
| Byrne, F., *et al*. [38] | Human patient | Adverse drug reaction | 5 mg once a day for 2 years and 6 months | A 9-year-old boy undergoing montelukast therapy for several years experienced neuropsychiatric events consisting of sleepwalking, sleep disturbance, bruxism and anxiety worsened by stressful events. |
| Anandan, N., *et al*. [41] | Human patient | Adverse drug reaction disappeared after stopping montelukast treatment | 10 mg once a day for 48 hour | 29-year-old asthmatic woman experienced auditory and visual hallucinations, which stopped within 2 days after montelukast withdrawal. |
| Alkhuja, S., *et al*. [42] | Human patient | Adverse drug reaction disappeared after stopping montelukast treatment | 10 mg once a day for 24 hour | 16-year-old female who showed daily parasomnias in the form of sleepwalking and sleep talking after taking montelukast and these parasomnias disappeared after discontinuing montelukast. |
| Callero, A., *et al*.[39] | Human patient | Adverse drug reaction disappeared after stopping montelukast treatment | 5 mg once a day for 3 weeks | Four children, aged between 1 and 5 years, developed sleep disorders as well as behavioural and mood disorders while receiving montelukast and after montelukast withdrawal, all these symptoms disappeared. |
| Kocyigit, A., *et al*. [43] | Human patient | Adverse drug reaction disappeared after stopping montelukast treatment | | 13-year-old patient reported visual hallucinations after starting a therapy with montelukast, which disappeared within 48 h after the cessation of drug intake. |

**TABLE 2: SUMMARY OF PROTECTIVE EFFECTS OF MONTELUKAST**

| Reference | Effect observed in | effect on organ/behavior | Dosage and duration of montelukast treatment | Conclusion |
|---|---|---|---|---|
| Abdel-Raheem, I.T., *et al*. [8] | Rats | Renoprotective against methotrexate treatment | 10 mg/kg for 10 days | Montelukast exhibited its renoprotective effect by normalization of kidney specific parameters, oxidative stress, and inflammatory mediators unbalanced by methotrexate treatment |
| Hasan, A., *et al*. [21] | Rats | hepatoprotective against radioactive iodine treatment | 10 mg/kg for 10 days | Montelukast treatment effectively protects the rat liver against damage caused by radioactive iodine treatment especially on hyperemia and capsule thickening. |
| Kuru, S., *et al*. [22] | Rats | protective effect on liver damage in obstructive jaundice | 10 mg/kg | Animal group receiving montelukast showed significantly less histopathological damage than control group. Myeloperoxidase, malondialdehyde, and total sulfhydryl level of liver also differed between montelukast and control group animals. |
| Beytur, A., *et al*. [7] | Rats | protective effect on cisplatin induced reproductive toxicity | 10 mg/kg for 10 days | Montelukast eliminates the effects of cisplatin on sperm motility, serum testosterone level, and on oxidative stress by increasing levels of GSH, CAT, GPx, and SOD levels. |

| | | | | |
|---|---|---|---|---|
| Azeem, E., *et al*. [9] | Rats | Protective against cadmium toxicity on pituitary gland | 10 mg/kg | Montelukast restored diminished hormonal level, increased MDA level and depleted oxidative enzymes on pituitary gland of rat exposed to cadmium. |
| Mansour, R.M., *et al*. [27] | Rats | Neuroprotective effect in rotenone-induced Parkinson's disease model | 10 mg/kg | Montelukast significantly attenuated motor impairment, decreased elevated oxidative stress mediators, declined p53 expression and improved the histopathological changes caused by rotenone. |
| Wu, S., *et al*. [24] | Rats | Montelukast attenuates intestinal ischemia-reperfusion injury | 2 and 20 mg/kg (single dose) | Montelukast reduces the expressions of CysLTR1 receptors which were otherwise increased due to ischemia in intestine, liver and kidney. |
| Yu, G., *et al*. [32] | Mice | Neuroprotective effect on cerebral ischemia in mice | 0.1 and 1.0 mg/kg (single dose) | Intraperitoneal injection of montelukast significantly attenuated all the ischemic insults |
| Sener, G., *et al*. [23] | Rats | renal protective effect against ischemia/ reperfusion | 10 mg/kg (single dose) | Montelukast treatment reversed all the biochemical indices as well as histopathological alterations induced by ischemia, and improved microscopic damage and renal function. It protects kidney tissue by balancing oxidant–antioxidant status, and regulating the generation of inflammatory mediators |
| Sener, G., *et al*. [25] | Rats | Protective effect against adverse effects of Alendronate | 10 mg/kg for 4 days | Montelukast prevented the damage as well as the changes in biochemical parameters in liver and kidney tissues studied, by its anti-inflammatory effect. |
| Marschallinger, J., *et al*. [33] | Rats | Montelukast improves cognition in old rats | 10 mg/kg for 42 days | It was found that montelukast reduces neuroinflammation and increases hippocampal neurogenesis through inhibition of the GPR17 receptor. It also restores learning and improve cognition in old rats. |
| Marschallinger, J., *et al*. [28] | Rats | Montelukast restores memory in animal model of dementia | 10 mg/kg for 42 days | It was found that montelukast reduces alpha-synuclein load and restores memory in an animal model of dementia with lewy bodies. |
| Kumar, A., *et al*. [26] | Rats | Neuroprotective effect of montelukast along with rofecoxib and caffeic acid against kainic acid induced cognitive dysfunction | 0.5 and 1 mg/kg for 14 days | Animal groups receiving treatment with montelukast, rofecoxib and caffeic acid showed improvement in memory performance, oxidative stress parameters and mitochondrial function as compared to that of control animals. |
| Zhang, C., *et al*.[34] | Mice | Protective effect on streptozotocin induced memory deficits | 1 or 2 mg/kg for 3 weeks | Oral treatment of montelukast for 3 weeks remarkably attenuated learning and memory impairments induced by streptozotocin. |
| Abdelzaher, L., *et al.* [35] | Mice | Montelukast alleviates autistic behavior induced by thimerosal treatment | 10 mg/kg for 3 weeks | Intraperitonial montelukast administration ameliorated thimerosal induced social deficit and inflammation. |

**Neuroprotective role of montelukast:**

Montelukast has shown neuroprotective activity in various animal studies[26-28]. It is a leukotriene receptor antagonist which binds to the CysLT1 and CysLT2 receptors, which are expressed in different brain regions namely hypothalamus, thalamus, putamen, pituitary, and medulla[29]. Increased levels of

leukotrienes in brain contribute to acute and chronic lesions[30]and in aged brain it may mediate neuroinflammatory responses including microglia activation[31].

Neuroprotective effect of montelukast was elucidated in a study on rotenone-induced Parkinson's disease rat model. Rotenone, a broad-spectrum insecticide treatment caused reduction in motor functioning and elevated oxidative stress markers. However, treatment with montelukast attenuated motor impairment, decreased the rise in oxidative stress mediators, declined p53 expression and showed improvement in the histopathological changes incited by rotenone[27].

In another study dose and time dependent neuroprotective effect of montelukast on cerebral ischemia in mice was observed. Intraperitoneal injection of montelukast one hour before the cerebral ischemia attenuated all the ischemic insults. However, post-treatment of montelukast (1 hour after cerebral ischemia) had no significant effect. Thus, these findings indicate toward therapeutic potential of montelukast in the treatment of cerebral ischemia at earlier phases[32].

In a study conducted on young (4 months) and old (20 months) rats it was found that montelukast reduces neuroinflammation and increases hippocampal neurogenesis through inhibition of the GPR17 receptor. It also restores learning and improves cognition in old rats. But no effect on cognition of young rat and on general behavior of both young and old rat was observed. This works findings concluded that montelukast might be a safe drug to restore cognitive functions in old individuals and for the treatment of dementias[33].

In a different study on a mice model of dementia with lewy bodies, it was found that treatment of montelukast reduces alpha-synuclein load and restores memory in mice. It was observed that cognitively deficient transgenic mice (expressing human wild-type alpha-synuclein) receiving 6-week treatment with montelukast showed increased tendency for learning compared to the control groups. Montelukast treatment caused modulation of beclin-1 expression which is a marker for autophagy, and in a reduction in the human alpha-synulcein load in the transgenic mice. This work suggests that montelukast by reducing the protein aggregation might be helpful in treating neurodegenerative diseases and dementia[28].

Neuroprotective effect of montelukast treatment along with rofecoxib and caffeic acid was evaluated against kainic acid. Kainic acid is a potent neuroexcitatory amino acid agonist, whose treatment induced cognitive dysfunction in rats. Significant improvement in memory performance, oxidative stress parameters and mitochondrial function was observed in animals receiving treatment with montelukast, rofecoxib and caffeic acid as compared to that of control animals[26].

Beneficial effect of montelukast on streptozotocin induced memory deficits in mice was also investigated. Streptozotocin is a toxic agent to beta cells of the pancreas in mammals. Intra-hippocampal microinfusion of streptozotocin caused learning and memory impairments, caused neuroinflammatory and apoptotic responses in hippocampus and up-regulated protein and mRNA of CysLT1R in hippocampus. Oral treatment of montelukast attenuated harmful effects induced by streptozotocin. Results of this study suggest that montelukast improves memory impairment and inhibits neuroinflammation and apoptosis in mice exposed and thus montelukast may provide a novel strategy for treating or preventing Alzheimer's disease[34].

In a recent study it was observed that montelukast is also useful in alleviating autistic behavior induced by thimerosal treatment in mice. Treatment of thimerosal, a mercury-containing organic compound impaired social activity and growth development in mice. However intraperitoneal montelukast administration ameliorated thimerosal induced social deficit. It also suppressed thimerosal induced toxicity and inflammation[35].

**Behavioral effects of montelukast:**

Number of human studies has reported behavioral changes during treatment with montelukast. In a study conducted on children receiving montelukast treatment, behavioural changes related to psychiatric disorders like nightmares, unspecified anxiety, aggressiveness, sleep disorders, insomnia, irritability, hallucination, hyperactivity and personality disorder were observed. In 80% of these reported cases, the duration from exposure to experiencing of adverse drug reaction was less than 1 week[36]. However, in a different study conducted on 30 children it was found that short-term (4 to 8 weeks) montelukast use is safe and do not cause any psychiatric problems in children[37].According to another data collected in Sweden during 1998-2007, it was indicated that out of 48 psychiatric adverse drug reaction induced due to montelukast, the most common were nightmares and hallucinations.

Apart from previously described psychiatric problems several cases of other adverse drug reactions have been reported like sleep disturbances and nightmares[38-40].Twenty four patient including adults and children, undergoing montelukast treatment reported nightmares[40].A 9-year-old boy undergoing montelukast therapy for several years experienced neuropsychiatric events consisting of sleepwalking, sleep disturbance, bruxism and anxiety worsened by stressful events[38].

Several cases have been reported in which adverse psychiatric effects disappeared after stopping montelukast treatment[41-43].An adult asthmatic woman reported auditory and visual hallucinations, which stopped within 2 days after montelukast withdrawal[41]. In another case, a child patient experienced visual hallucinations after starting a therapy with montelukast, which disappeared within 48 h after the cessation of drug intake[43].A female child showed daily parasomnias in the form of sleepwalking and sleep talking after taking montelukast and these parasomnias disappeared after discontinuing montelukast[25]. In another case it was observed that four children, aged between 1 and 5 years, developed sleep disorders (i.e. insomnia, somnolence and night terrors) as well as behavioural and mood disorders while receiving montelukast and after montelukast withdrawal, all these symptoms disappeared[39].

In previously discussed articles, both adults and children seem to develop psychiatric symptoms such as hallucinations, sleep walking, nightmares, anxiety, depression, aggression and headaches after the intake of the medication and symptoms becomes less after discontinuation of the therapy with montelukast.

**Montelukast as a potential treatment of COVID 19:**

Apart from previously discussed protective effects of montelukast, it has now emerged as a potential treatment of COVID 19. Studies have suggested that montelukast has improved COVID 19 prognosis as it possesses antiviral, anti-fibrosis properties and is protective against neuropsychiatric disorders[44-47].

Montelukast has shown antiviral properties against certain viral disease. It was found that montelukast inhibited Influenzae A virus gene expression by PERK phosphorylation. However, it did not alter viral RNA synthesis *in vitro* or viral RNA accumulation *in vivo*[44].In a study role of montelukast was investigated against hepatitis C virus. This study concluded that treatment of montelukast decreased the level of RNAs expressed by inhibiting viral replication[48]. In another study beneficiary action of montelukast against Zika virus was also reported. Montelukast treatment has been beneficial as it possesses antiviral properties and can antagonize cytokine storm[45].

In a study conducted on mice it was found that montelukast is also protective against respiratory syncytial virus. Viral infection induced cysLT release, which was decreased by montelukast treatment and it also attenuated viral induced inflammation and IFN-γ production in infected adult and neonate mice[49].

Many COVID 19 patients have been reported to experience central nervous system disorders involving headache, stroke, seizures and anosmia[47].On the other hand montelukast has shown neuroprotective effects in many animal studies. It been reported to improve recovery after brain ischemia, enhancing recruitment and maturation of oligodendrocyte precursor cells[50]. Additionally six week treatment of montelukast reduced neuroinflammation and elevated hippocampal neurogenesis through inhibition of the GPR17 receptor in younger and older rats with potential benefits for the prevention of manifestations such as delirium[33].

COVID-19 is also associated with increased risk of cytokine storm i.e., generation of both pro-inflammatory and anti-inflammatory cytokines by the innate immune system[51].Montelukast treatment causes decrease frequency and intensity of cytokine reactions[52]. Also, clinically, montelukast is used to reduce drug-related cytokine reactions induced by rituximab[52]and daratumumab[53].

COVID-19 may also result in pulmonary firbrosis or scar formation in lungs[54]. Montelukast is also known to possess anti fibrosis properties as it regulates the extracellular remodeling matrix and inhibits the formation of fibrosis. In a study protective effect of montelukast was investigated in bleomycin-induced pulmonary fibrosis[55]. In another study it was found that montelukast treatment attenuates bleomycin-induced inflammatory and oxidative lung injury and prevents lung fibrotic response[56].

As montelukast possess anti-inflammatory effects, suppress oxidative stress and reduce affect cytokine production, so it has been hypothesized that its treatment may limit progression of the disease on COVID-19 infection[46].

## CONCLUSION

In this review we highlighted that apart from being a commonly used drug for asthma treatment, montelukast also has neuroprotective potency. This review also focuses on therapeutic effectiveness of montelukast in COVID 19 treatment.

## CONFLICT OF INTEREST

There is no conflict of interest.

## REFERENCES

1. Peters-Golden, M., Gleason, M.M., & Togias, A. (2006). Cysteinyl leukotrienes: multi-functional mediators in allergic rhinitis. Clin. Exp. Allergy., 36(6):689–703.

2. Zubairi, A.B., Salahuddin, N., Khawaja, A., Awan, S., Shah, A.A., Haque, A. S., Husain, S.J., Rao, N., & Khan, J.A. (2013). A randomized, double-blind, placebo-controlled trial of oral montelukast in acute asthma exacerbation. BMC. Pulm. Med., 13:20.
3. Shirasaki, H., Kanaizumi, E., Seki, N., Fujita, M., Kikuchi. M., Himi. T. (2013). Localization and up-regulation of cysteinyl leukotriene-2 receptor in human allergic nasal mucosa. Allergol. Int., 62(2):223-228.
4. Bush, A. (2018). Management of asthma in children. Minerva. Pediatr., 70(5):444-457.
5. Haarman, M.G., van Hunsel, F., & de Vries, T.W. (2017). Adverse drug reactions of montelukast in children and adults. Pharmacol. Res. Perspect., 5(5):e00341.
6. Calapai, G., Casciaro, M., Miroddi, M., Calapai, F., Navarra, M., & Gangemi, S. (2014). Montelukast-induced adverse drug reactions: a review of case reports in the literature. Pharmacology., 94(1-2):60–70.
7. Beytur, A., Ciftci, O., Oguz, F., Oguzturk, H., & Yilmaz, F. (2012). Montelukast attenuates side effects of cisplatin including testicular, spermatological, and hormonal damage in male rats. Cancer. Chemother. Pharmacol., 69(1):207–213.
8. Abdel-Raheem, I.T., & Khedr, N.F. (2014). Renoprotective effects of montelukast, a cysteinyl leukotriene receptor antagonist, against methotrexate-induced kidney damage in rats. Naunyn. Schmiedebergs. Arch. Pharmacol., 387(4):341–353.
9. Abd-El-Azeem, E.K., Abass, M.F., Paulis, M.G., Nisreen, Abd-eltawab, Abd-Elgaber. (2017). Protective Effect of Montelukast against Cadmium Induced Pituitary Gland Toxicity. Int. J. Clin. Pharmacol. Toxicol., 6(2):256-261.
10. Russmann, S., Iselin, H.U., Meier, D., Zimmermann, A., Simon, H.U., Caduff, P., & Reichen, J. (2003). Acute hepatitis associated with montelukast. J. Hepatol., 38(5):694–695.
11. Actis, G.C., Bugianesi, E., Ottobrelli, A., & Rizzetto, M. (2007). Fatal liver failure following food supplements during chronic treatment with montelukast. Dig. Liver. Dis., 39(10):953–955.
12. Incecik, F., Onlen, Y., Sangun, O., & Akoglu, S. (2007). Probable montelukast-induced hepatotoxicity in a pediatric patient: case report. Ann. Saudi. Med., 27(6):462–463.
13. Harugeri, A., Parthasarathi, G., Sharma, J., D'Souza, G. A., & Ramesh, M. (2009). Montelukast induced acute hepatocellular liver injury. J. Postgrad. Med., 55(2):141–142.
14. Palodhi, S., Ray-Chaudhuri, P., Biswas, A., & Bera, T. (2012). Montelukast induced hypertriglyceridemia. Indian. Med. Gaz.,145(8):334-336.
15. Das, S., Mondal, S., Dey, J.K., Bandyopadhyay, S., Saha, I., & Tripathi, S.K. (2013). A case of montelukast induced hypercholesterolemia, severe hypertriglyceridemia and pancreatitis. J. Young. Pharm., 5(2):64–66.
16. Xie, J.X., Wei, J.F., & Meng, L. (2013). Montelukast sodium-induced hematuria: a case report and literature review of 19 cases in mainland China. Int. J. Clin. Pharmacol. Ther., 51(12):958–962.
17. Minciullo, P.L., Saija, A., Bonanno, D., Ferlazzo, E., & Gangemi, S. (2004). Montelukast-induced generalized urticaria. Ann. Pharmacother., 38(6):999–1001.
18. Herzinger, T., Ludolph-Hauser, D., & Przybilla, B. (2008). Urticaria triggered by antiallergy treatment. Clin. Exp. Dermatol., 33(4):519–520.
19. Aypak, C., Türedi, Ö., Solmaz, N., Yıkılkan, H., & Görpelioğlu, S. (2013). A rare adverse effect of montelukast treatment: ecchymosis. Respir. Care., 58(9):e104–e106.
20. Tayeb, MMS. (2013). Allergy to Montelukast Sodium Treated Effectively by Protracted Oral Desensitization: First Case Report. J. Aller. Ther., 4(1):129-133.
21. Atilgan, H.I., Yumusak, N., Sadic, M., Gultekin, S.S, Koca, G., Ozyurt, S., Demirel, K., & Korkmaz, M. (2015). Radioprotective effect of montelukast sodium against hepatic radioiodine (I-131) toxicity: A histopathological investigation in the rat model. Ankara. Üniv. Vet. Fak. Derg., 62(1):37-43.
22. Kuru, S., Kismet, K., Barlas, A. M., Tuncal, S., Celepli, P., Surer, H., Ogus, E., & Ertas, E. (2015). The Effect of Montelukast on Liver Damage in an Experimental Obstructive Jaundice Model. Viszeralmedizin., 31(2):131–138.
23. Sener, G., Sehirli, O., Velioğlu-Oğünç, A., Cetinel, S., Gedik, N., Caner, M., Sakarcan, A., & Yeğen, B.C. (2006). Montelukast protects against renal ischemia/reperfusion injury in rats. Pharmacol. Res., 54(1):65–71.
24. Wu, S., Zhu, X., Jin, Z., Tong, X., Zhu, L., Hong, X., Zhu, X., Liu, P., & Shen, W. (2015). The protective role of montelukast against intestinal ischemia-reperfusion injury in rats. Sci. Rep., 5:15787.
25. Sener, G., Kapucu, C., Cetinel, S., Cikler, E., & Ayanoğlu-Dülger, G. (2005). Gastroprotective effect of leukotriene receptor blocker montelukast in alendronat-induced lesions of the rat gastric mucosa. Prostaglandins. Leukot. Essent. Fatty. Acids., 72(1):1–11.
26. Kumar, A., Prakash, A., Pahwa, D., & Mishra, J. (2012). Montelukast potentiates the protective effect of rofecoxib against kainic acid-induced cognitive dysfunction in rats. Pharmacol. Biochem. Behav., 103(1):43–52.
27. Mansour, R.M., Ahmed, M., El-Sahar, A.E., & El Sayed, N.S. (2018). Montelukast attenuates rotenone-induced microglial activation/p38 MAPK expression in rats: Possible role of its antioxidant, anti-inflammatory and antiapoptotic effects. Toxicol. Appl. Pharmacol., 358:76–85.
28. Marschallinger, J., Altendorfer, B., Rockenstein, E., Holztrattner, M., Garnweidner-Raith, J., Pillichshammer, N., Leister, I., Hutter-Paier, B., Strempfl, K., Unger, M.S., Chishty, M., Felder, T., Johnson, M., Attems, J., Masliah, E., & Aigner, L. (2020). The Leukotriene Receptor Antagonist Montelukast Reduces Alpha-Synuclein Load and Restores Memory in an Animal Model of Dementia with Lewy Bodies. Neurotherapeutics., 17(3):1061–1074.
29. Heise, C.E., O'Dowd, B.F., Figueroa, D.J., Sawyer, N., Nguyen, T., Im, D.S., Stocco, R., Bellefeuille, J.N., Abramovitz, M., Cheng, R., Williams, D.L., Jr, Zeng, Z., Liu, Q., Ma, L., Clements, M.K., Coulombe, N., Liu, Y., Austin, C.P., George, S.R., O'Neill, G.P., Evans, J.F. (2000). Characterization of the human cysteinyl leukotriene 2 receptor. J. Biol. Chem., 275(39):30531–30536.

30. Hu, H., Chen, G., Zhang, J.M., Zhang, W.P., Zhang, L., Ge, Q.F., Yao, H.T., Ding, W., Chen, Z., & Wei, E.Q. (2005). Distribution of cysteinyl leukotriene receptor 2 in human traumatic brain injury and brain tumors. Acta. Pharmacol. Sin., 26(6):685–690.
31. Zhang, W.P., Hu, H., Zhang, L., Ding, W., Yao, H.T., Chen, K.D., Sheng, W.W., Chen, Z., & Wei, E.Q. (2004). Expression of cysteinyl leukotriene receptor 1 in human traumatic brain injury and brain tumors. Neurosci. Lett., 363(3):247–251.
32. Yu, G.L., Wei, E.Q., Zhang, S.H., Xu, H.M., Chu, L.S., Zhang, W.P., Zhang, Q., Chen, Z., Mei, R.H., & Zhao, M.H. (2005). Montelukast, a cysteinyl leukotriene receptor-1 antagonist, dose- and time-dependently protects against focal cerebral ischemia in mice. Pharmacology., 73(1):31–40.
33. Marschallinger, J., Schäffner, I., Klein, B., Gelfert, R., Rivera, F.J., Illes, S., Grassner, L., Janssen, M., Rotheneichner, P., Schmuckermair, C., Coras, R., Boccazzi, M., Chishty, M., Lagler, F. B., Renic, M., Bauer, H. C., Singewald, N., Blümcke, I., Bogdahn, U., Couillard-Despres, S., Aigner, L. (2015). Structural and functional rejuvenation of the aged brain by an approved anti-asthmatic drug. Nat. Commun., 6:8466.
34. Zhang, C.T., Lin, J.R., Wu, F., Ghosh, A., Tang, S. S., Hu, M., Long, Y., Sun, H.B., & Hong, H. (2016). Montelukast ameliorates streptozotocin-induced cognitive impairment and neurotoxicity in mice. Neurotoxicology., 57:214–222.
35. Abdelzaher, L.A., Hussein, O.A., & Ashry, I. (2021). The Novel Potential Therapeutic Utility of Montelukast in Alleviating Autistic Behavior Induced by Early Postnatal Administration of Thimerosal in Mice. Cell. Mol. Neurobiol., 41(1):129–150.
36. Wallerstedt, S.M., Brunlöf, G., Sundström, A., & Eriksson, A.L. (2009). Montelukast and psychiatric disorders in children. Pharmacoepidemiol. Drug. Saf., 18(9):858–864.
37. Donmez, Y.E, & Karaer, I.C. (2020). Does short-term montelukast treatment cause sleep problems or psychiatric problems in children? A preliminary study. Ann. Med. Res., 27(10):2654-2660.
38. Byrne, F., Oluwole, B., Whyte, V., Fahy, S., & McGuinness, D. (2012). Delayed Onset of Neuropsychiatric Effects Associated with Montelukast. Ir. J. Psychol. Med., 29(2):125–127.
39. Callero-Viera, A., Infante, S., Fuentes-Aparicio, V., Zapatero, L., & Alonso-Lebrero, E. (2012). Neuropsychiatric reactions to montelukast. J. Investig. Allergol. Clin. Immunol., 22(6):452–453.
40. Cereza, G., Garcia Doladé, N., & Laporte, J. R. (2012). Nightmares induced by montelukast in children and adults. Eur. Respir J., 40(6):1574–1575.
41. Anandan, N., & Ibitoye, F. (2008). Montelukast and worsening of hallucinations in paranoid schizophrenia. Psychol. Bull., 32(7):276.
42. Alkhuja, S., Gazizov, N., & Alexander, M.E. (2013). Sleeptalking! Sleepwalking! Side effects of montelukast. Case. Rep. Pulmonol., 2013;813786.
43. Kocyigit, A., Gulcan Oksuz, B., Yarar, F., Uzun, F., Igde, M., & Islek, I. (2013). Hallucination development with montelukast in a child with asthma: case presentation. Iran. J. Allergy. Asthma. Immunol., 12(4):397–399.
44. Landeras-Bueno, S., Fernández, Y., Falcón, A., Oliveros, J.C., & Ortín, J. (2016). Chemical Genomics Identifies the PERK-Mediated Unfolded Protein Stress Response as a Cellular Target for Influenza Virus Inhibition. mBio., 7(2):e00085–e16.
45. Chen, Y., Li, Y., Wang, X., & Zou, P. (2020). Montelukast, an Anti-asthmatic Drug, Inhibits Zika Virus Infection by Disrupting Viral Integrity. Frontiers in microbiology, 10:3079.
46. Fidan, C., & Aydoğdu, A. (2020). As a potential treatment of COVID-19: Montelukast. Med Hypotheses., 142:109828.
47. Mao, L., Jin, H., Wang, M., Hu, Y., Chen, S., He, Q., Chang, J., Hong, C., Zhou, Y., Wang, D., Miao, X., Li, Y., & Hu, B. (2020). Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. JAMA. Neurol., 77(6):683–690.
48. Ruiz, I., Nevers, Q., Hernández, E., Ahnou, N., Brillet, R., Softic, L., Donati, F., Berry, F., Hamadat, S., Fourati, S., Pawlotsky, J. M., & Ahmed-Belkacem, A. (2020). MK-571, a Cysteinyl Leukotriene Receptor 1 Antagonist, Inhibits Hepatitis C Virus Replication. Antimicrob. Agents. Chemother., 64(6):e02078-19.
49. Han, J., Jia, Y., Takeda, K., Shiraishi, Y., Okamoto, M., Dakhama, A., & Gelfand, E. W. (2010). Montelukast during primary infection prevents airway hyperresponsiveness and inflammation after reinfection with respiratory syncytial virus. Am. J. Respir. Crit. Car Med., 182(4):455–463.
50. Gelosa, P., Bonfanti, E., Castiglioni, L., Delgado-Garcia, J. M., Gruart, A., Fontana, L., Gotti, M., Tremoli, E., Lecca, D., Fumagalli, M., Cimino, M., Aigner, L., Abbracchio, M. P., & Sironi, L. (2019). Improvement of fiber connectivity and functional recovery after stroke by montelukast, an available and safe anti-asthmatic drug. Pharmacol. Res., 142:223–236.
51. Russell, B., Moss, C., George, G., Santaolalla, A., Cope, A., Papa, S., & Van Hemelrijck, M. (2020). Associations between immune-suppressive and stimulating drugs and novel COVID-19-a systematic review of current evidence. Ecancermedicalscience., 14:1022.
52. Kotchetkov, R., McLean, J., Nay, D., Gerard, L., Hopkins, S., & Didiodato, G. (2020). Premedication with montelukast and rupatadine decreased rituximab infusion time, rate, severity of reactions and use of rescue medications. Int. J. Can., 147(7):1979–1986.
53. Chari, A., Lonial, S., Mark, T. M., Krishnan, A. Y., Stockerl-Goldstein, K. E., Usmani, S. Z., Londhe, A., Etheredge, D., Fleming, S., Liu, B., Ukropec, J., Lin, T. S., Jagannath, S., & Nooka, A. K. (2018). Results of an early access treatment protocol of daratumumab in United States patients with relapsed or refractory multiple myeloma. Cancer., 124(22):4342–4349.

54. Peng, J., Zhou, H., Kuang, G., Xie, L., Tian, T., & Liu, R. (2017). The selective cysteinyl leukotriene receptor 1 (CysLT1R) antagonist montelukast regulates extracellular matrix remodeling. Biochem. Biophys. Res. Commun., 484(3):474–479.
55. Debelleix, S., Siao-Him Fa, V., Begueret, H., Berger, P., Kamaev, A., Ousova, O., Marthan, R., & Fayon, M. (2018). Montelukast reverses airway remodeling in actively sensitized young mice. Pediatr. Pulmonol., 53(6):701–709
56. Topaloğlu, N., Olgun Yıldızeli, Ş., Şener, G., Laçin, T., Şehirli, Ö., Bozkurtlar, E., Çelikel, Ç., & Ceyhan, B. (2018). Protective effect of cysteinyl leukotriene receptor antagonist montelukast in bleomycin-induced pulmonary fibrosis. Turk. Gogus. Kalp. Damar. Cerrahisi. Derg., 26(4):588–597.

**CITATION OF THIS ARTICLE**

Kaur M, & Sharma A. The potential neurobehavioral effects of an anti-asthmatic drug (Montelukast): A Review. Bull. Env. Pharmacol. Life Sci., Vol10[7] June 2021 :01-10