JSS ACADEMY OF HIGHER EDUCATION & RESEARCH
(DEEMED TO BE UNIVERSITY) MYSURU

CLINICAL PHARMACY NEWSLETTER

A Newsletter of Drug and Prescribing Information

Published by
Clinical Pharmacy Services Department, Govt. Medical College & Hospital, Ooty
(A Unit of Department of Pharmacy Practice, JSS College of Pharmacy, Ooty)

Volume XXVIII Issue 01 **January - March 2023**

INSIDE THIS ISSUE

Studying the Link between Rheumatoid Arthritis and Gut Dysbiosis

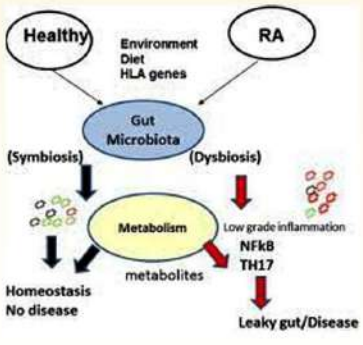
Rheumatoid arthritis (RA) is an autoimmune disease that affects the joints and may lead to disability. Recent advances have allowed us to study the human gut microbiota in great details. Numerous studies have shown that changes in gut microbiota may be playing a critical role in the pathogenesis of RA. RA is known to be caused by interaction of both genetic and environmental factors. RA has been classically known to be a disease of type III hypersensitivity reaction involving autoimmune antibodies called Rheumatoid factors (RF) . RF was thought to be the initiator of the disease, although now we know that some level of RF may be found even in individuals with no RA. Other autoantibodies have also been indicated to play a part in the pathogenesis of RA including anti-citrullinated protein antibodies (ACPAs), anti-peptidyl arginine deiminase-4 (anti-PAD-4), anti-carbamylated protein antibodies (anti-CarP), and anti-glucose-6-phosphate isomerase (anti-GPI). Twin studies have also shown that genetic inheritability may be playing a part in the development of RA, with one study showing the inheritability to be as high as 65%.

In recent years there has been a great interest among researchers on the study of gut microbiota and its effect on human diseases. Various successful studies on the changes in gut microbiota and consequent disease development has encouraged researchers to study the effect of gut dysbiosis on the development of autoimmune diseases even more. Numerous clinical studies have been performed to explore how the gut microbiota is affected in RA. When compared to healthy individuals, the gut microbiota of individuals with RA have been shown to have reduction in bacteria belonging to the Bifidobacertium and Bacteroides family, with an increase the species of the genus Prevotella. Scher et al, performed sequencing of 16S gene on d Eubacterium rectale–Clostridium coccoides. 114 fecal DNA samples, 44 of these samples were from patients with new onset RA. Results from this study showed that compared to healthy individuals, the samples from new onset RA patients had an increase in prevotella and decrease in Bacteroides subgroup.

Similar studies performed by Alpizar-Rodriguez et al. and Vaahtovuo et al. showed that individuals with preclinical RA had increased levels of Prevotella and decreased levels of Bacteroides subgroup, the genera Bifidobacterium and Eubacterium rectale–Clostridium coccoides.

TTTLooking at other microbial species, a study in China showed that RA patients had increased Ligilactobacillus salivarius in the intestines, in saliva, and on the teeth, while Haemophilus species were decreased in these sites. However, only in the first year following the commencement of RA was the amount of Prevotella in the stomach increased. The scientists demonstrated that the dysbiosis seen in RA patients partially improved after receiving treatment with disease-modifying medicines. Same study showed that the gut of RA patients was enriched with a large cluster of bacteria, including Gordonibacter pamelaeae, Clostridium asparagiforme, Eggerthella lenta, and Lachnospiraceae, as well as smaller clusters containing strains such Bifidobacterium dentium and Ruminococcus lactaris. Another study from China showed that RA patients had more fecal Lactobacillus species than healthy controls.

Since these studies suggest gut microbiota plays a part in the pathogenesis of RA, we can hypothesize that improving or altering gut microbiota could be used as a management option for RA patients. One way this could be achieved is by using probiotics. Probiotics is the use of live microorganisms to get a health benefit to the host. The efficacy of probiotics has been proven in mice studies. Inoculation of Clostridium, an indigenous intestinal microbiota, increased the number of T regulatory cells T (regs).



T (regs) are involved in down regulating inflammation, and their inoculation could reduce RA severity by suppressing inflammation. Oral administration of microbiota Lactobacillus casei in CIA rats decreased the levels of proinflammatory cytokines. Along with this, Lactobacillus casei treated rats also showed normal histopathology without any typical sign of RA such as synovial infiltration, pannus formation, cartilage, and bone destruction. Although it is challenging to establish a direct connection between gut dysbiosis and the risk of rheumatic diseases from case-control studies and cross-sectional research, experimental evidence suggests that gut dysbiosis may influence systemic immune responses, reduce tolerance, and result in autoimmunity.

Although it is challenging to establish a direct connection between gut dysbiosis and the risk of rheumatic diseases from case-control studies and cross-sectional research, experimental evidence suggests that gut dysbiosis may influence systemic immune responses, reduce tolerance, and result in autoimmunity.

"Gut dysbiosis can contribute to the onset of rheumatoid arthritis via multiple pathways"

Reference:

*Mohammad Zulqurnain Haider, "Studying the Link between Rheumatoid Arthritis and Gut Dysbiosis: A Mini Review", Advanced Gut & Microbiome Research, vol. 2022, Article ID 9695318, 5 pages, 2022.

*Li B, Selmi C, Tang R, Gershwin ME, Ma X. The microbiome and autoimmunity: a paradigm from the gut–liver axis. Cellular & molecular immunology. 2018 Jun;15(6):595-609.

*Yang X, Chang Y, Wei W. Emerging role of targeting macrophages in rheumatoid arthritis: Focus on polarization, metabolism and apoptosis. Cell proliferation. 2020 Jul;53(7):e12854.

*Picchianti-Diamanti A, Panebianco C, Salemi S, Sorgi ML, Di Rosa R, Tropea A, Sgrulletti M, Salerno G, Terracciano F, D'Amelio R, Laganà B. Analysis of gut microbiota in rheumatoid arthritis patients: disease-related dysbiosis and modifications induced by etanercept. International journal of molecular sciences. 2018 Sep 27;19(10):2938.

*Amdekar S, Singh V, Singh R, Sharma P, Keshav P, Kumar A. Lactobacillus casei reduces the inflammatory joint damage associated with collagen-induced arthritis (CIA) by reducing the pro-inflammatory cytokines: Lactobacillus casei: COX-2 inhibitor. Journal of clinical immunology. 2011 Apr;31:147-54.

Association between Sleep Duration and Left Ventricular Hypertrophy for Patients with Type 2 Diabetes Mellitus

Diabetes is a progressive disorder causing numerous complications, including small vessel or microvascular disease and large vessel or macrovascular disease. Microvascular complications could affect the kidney, retina, and peripheral nerves termed as diabetic nephropathy, diabetic retinopathy, and diabetic neuropathy, respectively. Diabetes has caused a tremendous economic burden in world. The estimated global direct health expenditure on diabetes in 2019 is USD 760 billion and is expected to grow to a projected USD 825 billion by 2030 and USD 845 billion by 2045. In the United States, the total cost of diabetes in 2017 was USD 327 billion and more than half of the expenditure was attributable to T2DM. Patients in the United States with diabetes incurred average medical expenditures of about USD 16,750 per year. China had one of the highest estimated total costs of diabetes with USD 109.0 billion.

Sleep is a public health concern affecting up to one-third of the population, and a large body of evidence has proved the association between insufficient sleep duration and quality and the risk of obesity, insulin resistance, and T2DM. As reported, sleep disorders are highly prevalent among patients with T2DM. Previous studies have proved a U-shaped association between sleep duration and incidence of T2DM, reporting 7-8 hours of sleep per night as the lowest risk. In observational studies, short sleep duration was associated with both a higher risk of incidence of T2DM and may also predict worse outcomes in those with existing diabetes. Experimental and clinical studies have suggested an independent association between obstructive sleep apnoea (OSA) and left ventricular mass (LVM), but there are few studies evaluating the impact of sleep duration on the LVM for diabetic patients.

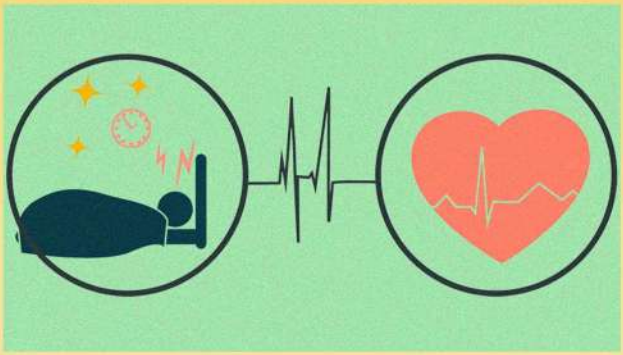
In present study, authors aimed to estimate the impact of sleep duration on the LVM for T2DM patients. This study was a large-scale single-center retrospective study performed at the Beijing Luhe Hospital. From October 2017 to February 2021, study team retrospectively reviewed 3074 consecutive patients undergoing transthoracic echocardiography (TTE) in the Center for Endocrine Metabolism and Immune Disease. All clinical data were acquired via a search of the Hospital Information System.

The information retrieved included age, gender, blood pressure (BP), heart rate (HR), height, weight, body mass index (BMI), diabetes duration, smoke history, alcohol intake history, hemoglobin (Hb), fasting blood glucose, hemoglobin A1C (HbA1c), blood lipid level, aminotransferase level, thyroid function and history of hypertension, hyperlipidemia, hyperuricemia (HUA), gout, coronary heart disease (CHD), and vascular disease. As reported, sleep duration was assessed by asking participants "What time do you usually go to bed? When get up?" and we calculated the sleep duration based on the results. Left ventricular hypertrophy (LVH), which can be measured by TTE, was represented by the left ventricular mass index (LVMI).

A total of 2689 T2DM patients were finally included in the study. Out of the 2689 patients, 655 (24.4%) patients were diagnosed with LVH and 2034 patients did not have LVH, who formed the control group. Baseline demographic information is given. The mean age was 51.8 ± 12.5 years; 56.2% were men; the mean BMI was 26.7 ± 4.0 kg/m2; the mean waist measurement was 94.3 ± 10.8 cm; the mean HR was 83.9 ± 12.6 bpm; the mean systolic blood pressure (SBP) was 132.6 ± 17.7 mmHg; the mean diastolic blood pressure (DBP) was 80.0 ± 11.9 mmHg; the mean sleep duration was 7.6 ± 1.4 hours per day. Of the participants, 1131 (42.1%) patients had hypertension, 1214 (45.1%) patients had hyperlipidemia, 312 (11.6%) had HUA, 59 (2.2%) had gout, and 347 (12.9%) had CHD. Patients with LVH were older than the control group (54.1 ± 12.1 vs. 51.2 ± 12.5 years, < 0.001) and had a longer duration of diabetes (88 (18–165) vs. 62 (7–133) months, $<$ 0.001). Patients with LVH slept more than the control group (7.8 ± 1.3 vs. 7.5 ± 1.4, < 0.001). Compared with the control group, patients who were diagnosed with LVH had a lower weight, lower height, lower BMI, lower waist, lower BP (SBP and DBP), lower triglyceride (TG), lower high-density lipoprotein cholesterol (HDL-c), lower low-density lipoprotein cholesterol (LDL-c), lower left ventricular ejective fraction (LVEF), higher Hb, higher alanine transaminase (ALT), higher creatinine (Cr), higher blood urea nitrogen (BUN), and higher uric acid (UA). Patients with LVH showed a higher prevalence of HUA and gout (< 0.05), while there were no significant differences in the history of hypertension, hyperlipidemia, or CHD.

"Sleep disturbance was associated with an increased risk for all CVD and CHD events, along with all-cause mortality in patients with new-onset type 2 diabetes"

Compared with the control group, patients with LVH were older and had a longer sleep duration per day. In the RCS model, the cut-off point of sleep duration was 8 hours per day. Multivariable analysis demonstrated that LVH was significantly correlated with a sleep duration of 8 hours per day (OR = 1.563, < 0.001), Hb (OR = 1.009, = 0.001), BUN (OR = 1.093, = 0.002), and HDL-c (OR = 0.612, = 0.001) for T2DM patients. To the authors knowledge, this is the first study evaluating sleep duration for the prediction of LVH. As a complication of common cardiovascular disorders (such as coronary atherosclerosis and myocardial infarction) and metabolism syndrome, LVH, which could progress to heart failure, needs early prevention and treatment.

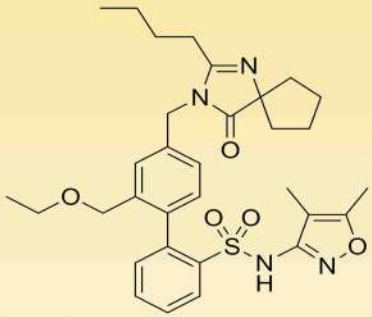


Authors are in the opinion that although many drug therapies, nutraceutical and dietary measures are available for the management of ventricular hypertrophy, most patients nonetheless experience a downhill course. Positive changes in lifestyle, a safe and inexpensive measure, may have merit in the management of ventricular hypertrophy, while the impact of sleep duration on ventricular hypertrophy remains to be fully understood. In the present study, we found that sleep duration may not be as long as possible, and a sleep duration longer than 8 hours may be one of the risk factors for ventricular hypertrophy. Authors also noted that several potential mechanisms may contribute to the association between long sleep duration and LVH. First, getting too much sleep can be a risk factor for hypertension, and hypertension is an important risk factor for cardiac hypertrophy. Sleep duration and BP are linked in a complex way. After adjusting for confounders such as age, BMI, and alcohol consumption, a U-shaped curve was reported between sleep duration and the risk of hypertension. Finally, study concludes that for patients with T2DM, long sleep duration (>8 hours per day), haemoglobin, BUN, and HDL-c were independently associated with LVH.

References:

Mu L, Li C, Zhao W, Li A, Zhao D, Zhang B. Association between Sleep Duration and Left Ventricular Hypertrophy for Patients with Type 2 Diabetes Mellitus. International Journal of Endocrinology. 2023. https://doi.org/10.1155/2023/5532778.

DRUG PROFILE
SPARSENTAN



Class: Dual endothelin and angiotensin II receptor antagonist.

Indication: Indicated to reduce proteinuria in adults with primary immunoglobulin A nephropathy (IgAN) at risk of rapid disease progression, generally a urine protein-to-creatinine ratio (UPCR) ≥1.5 g/g

Mechanism of Action:

Sparsentan is a molecule that acts as a dual antagonist of the endothelin type A receptor (ETAR) and the angiotensin II (Ang II) type 1 receptor (AT1R). It possesses two clinically validated mechanisms of action and selectively blocks the action of two potent vasoconstrictor and mitogenic agents, Ang II and endothelin 1 (ET-1), at their respective receptors. ET-1 and Ang II contribute to the pathogenesis of immunoglobulin A nephropathy (IgAN), a condition characterized by the increased production of galactose-deficient IgA1 (Gd-IgA1) antibodies. Gd-IgA1 antibodies lead to mesangial cell activation and proliferation, which stimulates and is stimulated by ET-1 and Ang II production. The pathological cycle of IgAN results in a compromised glomerular filtration barrier and subsequent proteinuria and haematuria. By acting as both an angiotensin receptor blocker (ARB) and an endothelin receptor antagonist (ERA), sparsentan reduces proteinuria in patients with IgAN. Sparsentan has a high affinity for both ETAR (Ki= 12.8 nM) and AT1R (Ki=0.36 nM), and greater than 500-fold selectivity for these receptors over the endothelin type B and angiotensin II subtype 2 receptors.

Dosage form and Administration:

Sparsentan is supplied as film-coated, modified oval, white to off-white tablets debossed on one side and plain on the other in the following strengths:

- 200 mg debossed with "105"
- 400 mg debossed with "021"

Instruct patient to swallow tablets whole with water prior to the morning or evening meal. Maintain the same dosing pattern in relationship to meals. If a dose is missed, take the next dose at the regularly scheduled time. Do not take double or extra doses.

Dosing in Renal & Hepatic Impairment:

Renal impairment

*Mild-to-moderate (eGFR 30-89 mL/min/1.73 m2): No clinically significant differences in pharmacokinetics observed

*Severe (eGFR <30 mL/min/1.73 m2): Not studied

Hepatic impairment

*Mild, moderate, or severe (Child-Pugh A-C): Avoid use with any hepatic impairment because of risk of serious liver injury.

Pharmacokinetics:

The pharmacokinetics of sparsentan are presented as geometric mean (% coefficient of variation) unless otherwise specified. The Cmax and AUC of sparsentan increase less than proportionally following administration of single doses of 200 mg to 1600 mg. Sparsentan showed time-dependent pharmacokinetics which may be related to the drug inducing its own metabolism over time. Steady-state plasma levels are reached within 7 days with no accumulation of exposure at the approved recommended dosage. Following a single oral dose of 400 mg sparsentan, the mean Cmax and AUC are 6.97 µg/mL and 83 µg×h/mL, respectively. Following daily doses of 400 mg sparsentan, the steady-state mean Cmax and AUC are 6.47 µg/mL and 63.6 µg×h/mL, respectively. Following a single oral dose of 400 mg sparsentan, the median (minimum to maximum) time to peak plasma concentration is approximately 3 hours (2 to 8 hours). The apparent volume of distribution at steady state is 61.4 L at the approved recommended dosage. Sparsentan is >99% bound to human plasma proteins. The apparent clearance (CL/F) of sparsentan is 3.88 L/h following the initial 400 mg dose then increases to 5.11 L/h at steady state. The half-life of sparsentan is estimated to be 9.6 hours at steady state. Cytochrome P450 3A is the major isozyme responsible for the metabolism of sparsentan. After a single dose of radiolabeled sparsentan 400 mg to healthy subjects, approximately 80% of the dose was recovered in feces (9% unchanged) and 2% in urine (negligible amount unchanged). 82% of the dosed radioactivity was recovered within a 10-day collection period.

Adverse Reactions:

Clinically significant adverse reactions of sparsentans are

- Hepatotoxicity
- Embryo-Fetal Toxicity
- Hypotension
- Acute Kidney Injury
- Hyperkalemia
- Fluid Retention

Contraindications:

Use of Sparsentan is contraindicated in patients who are pregnant.
Do not coadminister Sparsentan with angiotensin receptor blockers (ARBs), ERAs, or aliskiren.

Precautions:

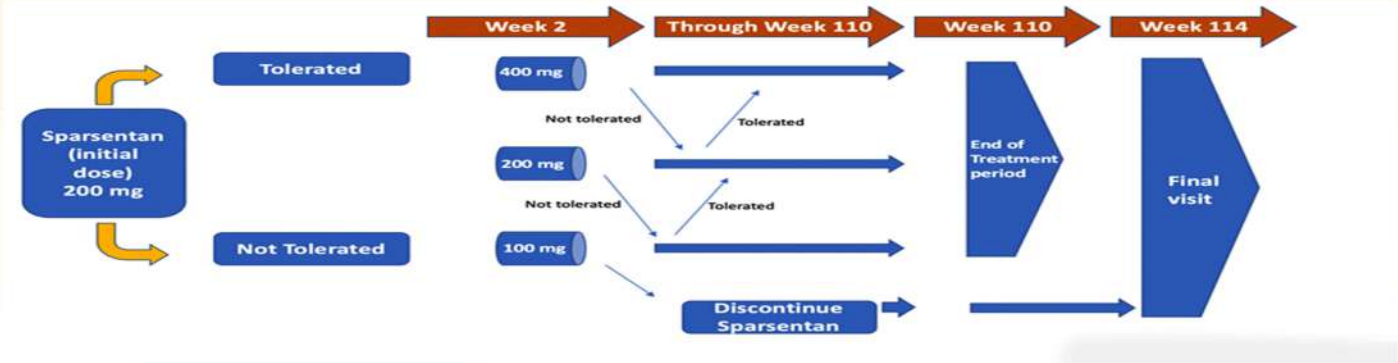
- Do not use this medicine together with aliskiren (Tekturna®) or other blood pressure medicine (eg, angiotensin receptor blocker, endothelin receptor blocker).
- Using this medicine while pregnancy can harm the unborn baby. For are a woman who can get pregnant, the doctor's will do tests before starting, during treatment, and 1 month after stopping this medicine to make sure the patient is not pregnant. Use an effective form of birth control before starting, during treatment, and for 1 month after your final dose to keep from getting pregnant. Consult the physician to decide the drug taking for birth control.
- This medicine may cause serious liver problems and may cause dark urine, fatigue, loss of appetite, nausea or vomiting, severe stomach pain, or yellow eyes or skin.
- This medicine may cause serious kidney problems and may cause agitation, coma, confusion, decreased urine output, depression, dizziness, headache, hostility, irritability, lethargy, muscle twitching, nausea, rapid weight gain, seizures, stupor, swelling of the face, ankles, or hands, or unusual tiredness or weakness.
- Check with the doctor right away if they experincing confusion, irregular heartbeat, nausea or vomiting, nervousness, numbness or tingling in the hands, feet, or lips, stomach pain, trouble breathing, or weakness or heaviness of the legs. These may be symptoms of hyperkalemia (high potassium in the blood).
- This medicine may cause fluid retention (too much water in the body). Check with the doctor right away if they have decrease in amount of urine, noisy, rattling, or trouble breathing, swelling of the face, hands, feet, or lower legs, or weight gain.
- Do not take other medicines unless they have been discussed with the physician. This includes prescription or nonprescription (over-the-counter [OTC]) medicines and herbal or vitamin supplements.

Drug Interactions:

- Do not coadminister SPARSENTAN with ARBs, ERAs, or aliskiren. Do not coadminister SPARSENTAN with ARBs, ERAs, or aliskiren.
- Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inhibitor increases sparsentan Cmax and AUC, which may increase the risk of sparsentan adverse reactions.
- Avoid concomitant use with a strong CYP3A inducer. Sparsentan is a CYP3A substrate. Concomitant use with a strong CYP3A inducer decreases sparsentan Cmax and AUC, which may reduce sparsentan efficacy.
- Avoid concomitant use of acid reducing agents (histamine H2 receptor antagonist and PPI proton pump inhibitor) with sparsentan. Sparsentan exhibits pH-dependent solubility. Antacids or acid reducing agents may decrease sparsentan exposure which may reduce sparsentan efficacy.
- Sparsentan is an inducer of CYP2B6, 2C9, and 2C19. Sparsentan decreases exposure of these substrates, which may reduce efficacy related to these substrates.
- Sparsentan is an inhibitor of P-gp and BCRP. Sparsentan may increase exposure of these transporter substrates, which may increase the risk of adverse reactions related to these substrates.
- Concomitant use of sparsentan with potassium-sparing diuretics, potassium supplements, potassium-containing salt substitutes, or other drugs that raise serum potassium levels may result in hyperkalemia.

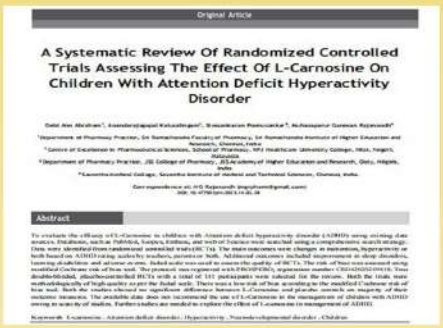
Reference

- Rovin BH, Barratt J, Heerspink HJ, Alpers CE, Bieler S, Chae DW, Diva UA, Floege J, Gesualdo L, Inrig JK, Kohan DE. Efficacy and safety of sparsentan versus irbesartan in patients with IgA nephropathy (PROTECT): 2-year results from a randomised, active-controlled, phase 3 trial. The Lancet. 2023;402(10417):2077-90.
- Chiu AW, Bredenkamp N. Sparsentan: A First-in-Class Dual Endothelin and Angiotensin II Receptor Antagonist. Ann Pharmacother. 2023.



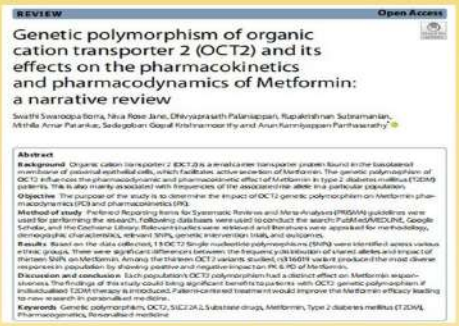
Publications from Department of Pharmacy Practice (January to March 2023)

- Abraham DA, Kalusalingam A, Ponnusankar S, Rajanandh MG. A Systematic Review Of Randomized Controlled Trials Assessing The Effect Of L-Carnosine On Children With Attention Deficit Hyperactivity Disorder. Journal of Pharmaceutical Negative Results. 2023;14(02): 224 – 230.
- Borra SS, Jane NR, Palaniappan D, Subramanian R, Patankar MA, Krishnamoorthy SG, Parthasarathy AK. Genetic polymorphism of organic cation transporter 2 (OCT2) and its effects on the pharmacokinetics and pharmacodynamics of Metformin: a narrative review. Egyptian Journal of Medical Human Genetics. 2023;24(1):13.
- Swathi Swaroopa B, Varghese R, Krishnamoorthy SG, Abdalla HE, Baiju A, Borra SS. A systematic review of preclinical animal studies on fenofibrate's potential role in type 1 diabetic micro-vascular complications. Brazilian Journal of Pharmaceutical Sciences. 2023, 58: e210332:1-11.
- Borra SS, Shaji JR, Manomohan A, Koshy E, Krishnamoorthy SG. Efficacy of mindfulness meditation in psychological distress exacerbated tinea cruris: A case report. Journal of Applied Pharmaceutical Science. 2023;13(2):192-5.
- Uma KV, Martin JV, Sutheeswaran G, Rajeshkumar R, Ponnusankar S. Molecular docking and *in-silico* predictive analysis of potential herb-drug interactions between *Momordica charantia* and Empagliflozin. Journal of Applied Pharmaceutical Science. 2023;13(3):175-82.


Original Article

A Systematic Review Of Randomized Controlled Trials Assessing The Effect Of L-Carnosine On Children With Attention Deficit Hyperactivity Disorder

Abstract


REVIEW Open Access

Genetic polymorphism of organic cation transporter 2 (OCT2) and its effects on the pharmacokinetics and pharmacodynamics of Metformin: a narrative review

Abstract


BJPS

Brazilian Journal of Pharmaceutical Sciences

A systematic review of preclinical animal studies on fenofibrate's potential role in type 1 diabetic micro-vascular complications


Journal of Applied Pharmaceutical Science Vol. 13(03), pp 175-182, March, 2023

Molecular docking and in-silico predictive analysis of potential herb-drug interactions between *Momordica charantia* and Empagliflozin

ARTICLE INFO

ABSTRACT


Journal of Applied Pharmaceutical Science Vol. 13(02), pp 192-195, February, 2023

Efficacy of mindfulness meditation in psychological distress exacerbated tinea cruris: A case report

ARTICLE INFO

ABSTRACT

Important Dates to Remember

For clarifications/ feedback, write to:

The Chief Editor
Clinical Pharmacy Newsletter,
Department of Pharmacy Practice

Prepared & Circulated by:

Department of Pharmacy Practice
JSS College of Pharmacy,
Rocklands, Udhagamandalam- 643001
The Nilgiris Tamilnadu, India
E-mail ID: pharmacypracticeooty@gmail.com
/drsponnusankar@jssuni.edu.in
Phone: (+91)-423-2443393
Fax: (+91)-423-2442937