Publications Template

#	Research Title	Field	Abstract	Year of Publication Publishing	Publishing Link "URL"
1	The Anti-inflammatory & Apoptotic effects of Atorvastatin in combination with Celecoxib in Adjuvant Induced Arthritis in rats. (Journal of Pharmacy and Pharmacology)	Pharmacology	Statins seem to have anti-inflammatory effects independent of their lipid-lowering abilities. Previous studies demonstrated a strong synergy between statins and non-steroidal anti-inflammatory drugs in growth inhibition and apoptosis induction in cultured cancer cells. This study aimed at evaluating the combined anti-inflammatorty and apoptotic effects of atorvastatin and celecoxib in adjuvant-induced arthritis in rats. Adjuvant arthritis was induced in Sprague-Dawley rats by intradermal injection of 0.1 ml suspension of heat-killed Mycobacterium butyricum (12 mg/ml) in incomplete Freund's adjuvant. Rats were treated orally with atorvastatin (10 mg/kg/day), celecoxib (3 mg/kg/day) and their combination from day 12 to day 27 post-adjuvant injection. Arthritis progression was assessed by hind paw swelling and arthrogram scores. Serum levels of C-reactive protein (CRP), tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10) and vascular endothelial growth factor (VEGF) were measured. Caspase-3 activity and DNA fragmentation were determined in tibiotarsal joints tissue to evaluate apoptosis.	2013	

			Celecoxib proved to be more effective, than atorvastatin in suppressing clinical severity of arthritis, reducing serum levels of VEGF, CRP and TNF-α and increasing serum levels of IL-10. Caspase-3 activity and DNA fragmentation were more significantly enhanced by atorvastatin. Combining atorvastatin and celecoxib provided higher efficacy, in reducing inflammation and inducing apoptosis, than either agent alone.		
2	Astrocyte-Targeted Transporter-Utilizing Derivatives of Ferulic Acid Can Have Multifunctional Effects Ameliorating Inflammation and Oxidative Stress in the Brain. (Oxidative medicine and cellular longevity)	Pharmacology	Ferulic acid (FA) is a natural phenolic antioxidant, which can exert also several other beneficial effects to combat neuroinflammation and neurodegenerative diseases, such as Alzheimer's disease. One of these properties is the inhibition of several enzymes and factors, such as β-site amyloid precursor protein (APP) cleaving enzyme 1 (BACE1), cyclooxygenases (COXs), lipoxygenases (LOXs), mammalian (or mechanistic) target for rapamycin (mTOR), and transcription factor NF-κB. We have previously synthesized three L-type amino acid transporter 1- (LAT1-) utilizing FA-derivatives with the aim to develop brain-targeted prodrugs of FA. In the present study, the cellular uptake and bioavailability of these FA-derivatives were evaluated in mouse primary astrocytic cell cultures together with their inhibitory effects towards BACE1, COX/LOX, mTOR, NF-κB, acetylcholinesterase (AChE), and oxidative stress. According to the results, all three FA-derivatives were taken up 200–600 times more effectively at 10 μM concentration into the astrocytes than FA, with one derivative having a high intracellular	2019	https://doi.org/10.1155/2019/3528148.

			bioavailability, particularly at low concentrations. Moreover, all of the derivatives were able to inhibit BACE1, COX/LOX, AChE, and oxidative stress measured as decreased cellular lipid peroxidation. Furthermore, one of the derivatives modified the total mTOR amount. Therefore, these derivatives have the potential to act as multifunctional compounds preventing β-amyloid accumulation as well as combating inflammation and reducing oxidative stress in the brain. Thus, this study shows that converting a parent drug into a transporter-utilizing derivative not only may increase its brain and cellular uptake, and bioavailability but can also broaden the spectrum of pharmacological effects elicited by the derivative.		
3	Sitagliptin and tofacitinib ameliorate adjuvant induced arthritis via modulating the cross talk between JAK/STAT and TLR-4/NF-κB signaling pathways. (Lifesciences Journal)	Pharmacology	**Aims** Rheumatoid arthritis is an autoimmune systemic disorder causing pain, swelling, stiffness, and disability in various joints. This work was designed to evaluate the effect of sitagliptin and tofacitinib on Janus kinase (JAK)/signaling transducer and activator of transcription (STAT) and toll like receptor (TLR-4)/nuclear factor kappa B (NF-κB) signaling pathways in adjuvant induced arthritis in rats. **Materials and methods** Severity of arthritis was evaluated and serum was analyzed for inflammatory mediators. The mRNA and protein expression level of the most important members of the two signaling pathways were determined. Lipid profile, transaminases and renal function parameters were assessed.	2020	https://doi.org/10.1016/j.lfs.2020.118261.

			Key findings Sitagliptin and tofacitinib significantly decreased the level of inflammatory parameters, the mRNA and protein expression level of the members of JAK/STAT and TLR-4/NF-κB pathways with more prominent effect of sitagliptin on TLR-4/NF-κB pathway and more expected obvious effect of tofacitinib on JAK/STAT pathway. The combination offered additional anti-inflammatory effect by inhibiting the cross talk between these pathways as inhibition of NF-κB activation decreased the serum level of IL-6 preventing the activation of STAT-3 in tibiotarsal tissues. **Significance** The combination of tofacitinib and sitagliptin normalized serum lipids and blood glucose level which could offer protection against cardiovascular diseases and caused partial reversal of serum transaminases and creatinine levels which can protect against tofacitinb's related hepato and nephrotoxicity. We could conclude that the combination of Sitagliptin with tofacitinib can offer synergistic anti-inflammatory effect and more protective action against side effects of tofacitinib.		
4	Metformin and omega-3 fish oil elicit anti-inflammatory effects via modulation of some dysregulated micro RNAs	Pharmacology	**Objective** Rheumatoid arthritis is a progressive inflammatory disease with multiple dysfunctional intracellular signaling pathways that necessitate new approaches for its management. Hence, the study aimed to inspect the ability of the combination therapy of metformin and omega-3 to modulate different signaling pathways and micro RNAs such as (miR-	2021	https://doi.org/10.1016/j.intimp.2020.107362.

	expression and signaling pathways in experimental induced arthritis. (International Immunopharmacology journal)		155, miR-146a and miR-34) as new targets in order to mitigate adjuvant-induced arthritis and compare their effect to that of methotrexate. **Methods** Fourteen days post adjuvant injection, Sprague-Dawley rats were treated orally with metformin (200 mg/kg/day) and/or omega-3 (300 mg/kg/day) or intraperitoneally with methotrexate (2 mg/kg/week) for 4 weeks. **Results and conclusion** All drug treatments amended the arthrogram score and hind paw swelling as well as decreased serum tumor necrosis factor (TNF)-α and interleukin (IL)-1β levels. On the molecular level, all therapies activated phospho-5′adenosine monophosphate-activated protein kinase (p-AMPK) and protein phosphatase 2A (PP2A), while they inhibited phospho-mammalian target of rapamycin (p-mTOR), phospho-signal transducers and activators of transcription (p-STAT3), nuclear factor (NF)-κB p65 subunit, phosho38 mitogen-activated protein kinase (p38 MAPK) and phospho- c-Jun N-terminal kinase (p-JNK). In addition, they decreased the elevated expression level of miRNA-155, 146a and increased the expression level of miRNA-34 and they decreased the expression level of retinoic acid receptor related orphan receptor γT (RORγT) and increased that of fork head box P3 (FOXP3), correcting Th17/Treg cells balance. On most of the aforementioned parameters, the effect of the combination therapy was comparable to that of methotrexate, emphasizing that this combination		

			possesses better additive anti-inflammatory effect than either drug when used alone. In addition, the combination was capable of normalizing the serum transaminases levels as compared to untreated group offering hepatoprotective effect and suggesting the possibility of its use as a replacement therapeutic strategy for MTX in rheumatoid arthritis.		
5	Orchestrated modulation of rheumatoid arthritis via crosstalking intracellular signaling pathways. (Inflammopharmacology Journal)	Pharmacology	Cell signaling is considered a part of a network for communication that regulates basic cellular activities. The ability of cells to communicate correctly to the surrounding environment has an important role in development, tissue repair, and immunity as well as normal tissue homeostasis. Dysregulated activation and crosstalk between many intracellular signaling pathways are implicated in the pathogenesis of rheumatoid arthritis (RA), such as the Janus Kinase/signal transducers and activators of transcription (JAK/STAT), Toll-like receptor/nuclear factor kappa B (TLR/NF-κB), phosphatidylinositide-3Kinase/protein kinase B/mammalian target of rapamycin (PI-3K/AKT/mTOR), the stress activated protein kinase/mitogen-activated protein kinase (SAPK/MAPK), and spleen tyrosine kinase (SYK) pathways. Other interrelated pathways that can be targeted to halt the inflammatory status in the disease are purinergic 2X7 receptor (P2X7R)/nucleotide binding oligomerization domain-like receptor family pyrin domain containing 3 or inflammasome (NLRP-3)/NF-κB and Notch pathways. In this review, we will show	2021	https://doi.org/10.1007/s10787-021-00800-3.

			the orchestrated modulation in the pathogenesis of RA via the crossregulation between dysregulated signaling pathways which can mediate a sustained loop of activation for these signaling pathways as well as aggrevate the inflammatory condition. Also, this review will highlight many targets that can be useful in the development of more effective therapeutic options.		
6	Micro RNAs 26b, 20a inversely correlate with GSK-3 β/NF-κB/NLRP-3 pathway to highlight the additive promising effects of atorvastatin and quercetin in experimental induced arthritis. (International Immunopharmacology journal)	Pharmacology	Rheumatoid arthritis (RA) is an inflammatory disease with challenging therapeutic potential due to the implication of cross-talking intracellular pathways in the pathogenesis of the disease. This study aimed to evaluate the effects of the combination therapy of atorvastatin and quercetin on glycogen synthase kinase-3 beta/ nuclear factor kappa-B/ nucleotide-binding oligomerization domain-like receptor family pyrin domain containing-3 or inflammasome (GSK-3β/NF-KB/NLRP-3) pathway as well as on microRNAs 26b and 20a (miR-26b, miR-20a) and to investigate the possible beneficial outcomes of the combination to offer a better treatment option than methotrexate (MTX) in adjuvant-induced arthritis (AIA). Assessment of arthritis progression, serum inflammatory, and oxidative parameters were done. The tibiotarsal tissue expression of the inflammatory parameters was evaluated. Western blot analysis was done to assess the expression level of the important members in the GSK-3β/NF-κB/NLRP-3 pathway. Furthermore, the expression level of both microRNAs and serum level of transaminases were determined. All treatments,	2021	https://doi.org/10.1016/j.intimp.2021.108042.

			especially the combination regimen, abated arthritis progression, the elevated serum level of inflammatory and oxidative stress parameters in arthritic rats. Moreover, they down-regulated the gene expression of the important members of the aforementioned signaling pathway, amended the tissue levels of inflammatory parameters and elevated the expression level of miR-26b and miR-20a. Finally, we concluded that the combination therapy modulated miR-26b and miR-20a as well as GSK-3β/NF-κB/NLRP-3 pathway, provided additive anti-inflammatory and anti-oxidant effects and offered an additional hepatoprotective effect as compared to untreated arthritic rats and MTX-treated groups, suggesting its promising role to be used as replacement therapy to MTX in RA.		
7	"Anti-neoplastic action of Cimetidine/Vitamin C on histamine and the PI3K/AKT/mTOR pathway in Ehrlich breast cancer" Scientific Reports journal	Pharmacology	The main focus of our study is to assess the anti-cancer activity of cimetidine and vitamin C via combating the tumor supportive role of mast cell mediators (histamine, VEGF, and TNF-α) within the tumor microenvironment and their effect on the protein kinase A(PKA)/insulin receptor substrate-1(IRS-1)/phosphatidylinositol-3-kinase (PI3K)/serine/threonine kinase-1 (AKT)/mammalian target of rapamycin (mTOR) cue in Ehrlich induced breast cancer in mice. In vitro study was carried out to evaluate the anti-proliferative activity and combination index (CI) of the combined drugs. Moreover, the Ehrlich model was induced in mice via subcutaneous injection of Ehrlich ascites carcinoma cells (EAC) in the mammary fat pad, and then they were left for 9	2022	publication in progress

			days to develop obvious solid breast tumor. The combination therapy possessed the best anti-proliferative effect, and a CI <1 in the MCF7 cell line indicates a synergistic type of drug interaction. Regarding the in vivo study, the combination abated the elevation in the tumor volume, and serum tumor marker carcinoembryonic antigen (CEA) level. The serum vascular endothelial growth factor (VEGF) level and immunohistochemical staining for CD34 as markers of angiogenesis were mitigated. Additionally, it reverted the state of oxidative stress and inflammation. Meanwhile, it caused an increment in apoptosis, which prevents tumor survival. Furthermore, it tackled the elevated histamine and cyclic adenosine monophosphate (cAMP) levels, preventing the activation of the (PKA/IRS-1/PI3K/AKT/mTOR) cue. Finally, we concluded that the synergistic combination provided a promising anti-neoplastic effect via reducing the angiogenesis, oxidative stress, increasing apoptosis,as well as inhibiting the activation of PI3K/AKT/mTOR cue, and suggesting its use as a treatment option for breast cancer.		