Publications Template

#	Research Title	Field	Abstract	Year of Publication Publishing	Publishing Link "URL"
1.	Hyaluronic acid/diminazene aceturate combination ameliorates osteoarthritic anomalies in a rodent model: a role of the ACE2/Ang1-7/MasR axis.	Autoimmune Pharmacology	The implication of the tissue-localized renin-angiotensin system (RAS) in the pathogenesis of osteoarthritis (OA) has been documented in the last decades. A combination of intraarticular (IA) corticosteroid and hyaluronic acid (HYAL) is approved for pain relief in patients with mild to moderate OA. Combining HYAL with an activator of angiotensin-converting enzyme 2, diminazen aceturate (DIZE), was evaluated in this study for its therapeutic potential. Monosodium iodoacetate was used to induce OA. The effects of daily administration of DIZE versus once-per-week IA injection of HYAL and a combination of both drugs for 21 days on OA deformities in rats' knees were observed. Evaluation of motor activities, pain, and inflammatory response was done using rotarod, knee bend, and knee swelling tests. RAS components, inflammatory biomarkers, and oxidative stress mediators were measured in the knee joint. X-ray radiological examination and histopathological investigations were used to assess joint degeneration and regeneration. Levels of both inflammatory and oxidative markers in knee joint homogenate of OA rats rose, and these increments were mostly improved by the three therapies with a more prominent effect of the drug combination, an effect that was also reflected in the behavioral tests. RAS markers have shown better responsiveness to the combination therapy over	2023	https://link.springer.com/article/10.1007/s10787-023-01335-5

			both drugs individually, showing a pronounced increase in the angiotensin 1–7 amount. Both radiological and histopathology investigations came to confirm the biochemical results, nominating a combination of HYAL and DIZE as a possible therapeutic option for OA.		
2.	Morin suppresses mTORc1/IRE-1α/JNK and IP3R-VDAC-1 pathways: Crucial mechanisms in apoptosis and mitophagy inhibition in experimental Huntington's disease, supported by in silico molecular docking simulations	Autoimmune Pharmacology	**Aims** Endoplasmic reticulum stress (ERS) with aberrant mitochondrial-ER contact (MERC), mitophagy, and apoptosis are interconnected determinants in neurodegenerative diseases. Previously, we proved the potential of Morin hydrate (MH), a potent antioxidant flavonoid, to mitigate Huntington's disease (HD)-3-nitropropionic acid (3-NP) model by modulating glutamate/calpain/Kidins220/BDNF trajectory. Extending our work, we aimed to evaluate its impact on combating the ERS/MERC, mitophagy, and apoptosis. **Methods** Rats were subjected to 3-NP for 14 days and post-treated with MH and/or the ERS inducer WAG-4S for 7 days. Disease progression was assessed by gross inspection and striatal biochemical, histopathological, immunohistochemical, and transmission electron microscopical (TEM) examinations. A molecular docking study was attained to explore MH binding to mTOR, JNK, the kinase domain of IRE1-α, and IP3R. **Key findings** MH decreased weight loss and motor dysfunction using open field and rotarod tests. It halted HD degenerative striatal neurons and nucleus/mitochondria ultra-microscopic alterations reflecting neuroprotection. Mechanistically, MH deactivated striatal mTOR/IRE1-α/XBP1s&JNK/IP3R, PINK1/Ubiquitin/Mfn2, and cytochrome c/caspase-3 signaling	2023	https://www.sciencedirect.com/science/article/pii/S0024320523009979

			pathways, besides enhancing p-PGC-1α and p-VDAC1. WAG-4S was able to ameliorate all effects initiated by MH to different extents. Molecular docking simulations revealed promising binding patterns of MH and hence its potential inhibition of the studied proteins, especially mTOR, IP3R, and JNK. **Significance** MH alleviated HD-associated ERS, MERC, mitophagy, and apoptosis. This is mainly achieved by combating the mTOR/IRE1-α signaling, IP3R/VDAC hub, PINK1/Ubiquitin/Mfn2, and cytochrome c/caspase 3 axis to be worsened by WAG-4S. Molecular docking simulations showed the promising binding of MH to mTOR and JNK as novel identified targets.		
3.	Diminazene aceturate or losartan ameliorates the functional, radiological and histopathological alterations in knee osteoarthritis rodent model: repurposing of the ACE2/Ang1-7/MasR cascade	Autoimmune Pharmacology	**Purpose** Current therapies for osteoarthritis (OA) are limited to analgesics and anti-inflammatory drugs. Considering the importance of oxidative stress and inflammatory mediators in OA etiology, we tested the hypothesis that targeting the renin–angiotensin–aldosterone system (RAAS) can improve OA anomalies. Diminazene (DIZE), an activator of angiotensin-converting enzyme 2 and the angiotensin 2 type-1 receptor blocker losartan (LOS) were used for this purpose. **Methods** OA was induced by a single intra-articular injection of monosodium iodoacetate. The effects of exposure to DIZE or LOS for 21 days on OA anomalies in rats' knees were investigated. Evaluation of motor function, nociception, and inflammatory response was done using rotarod, knee bend and knee swelling tests. Markers of knee joint inflammation, and	2023	https://link.springer.com/article/10.1186/s40634-023-00673-1

			cellular oxidation in addition to the RAAS biomarkers, were assessed in knee tissues, along with radiological and histopathological investigations. **Results** Elevations in inflammatory and oxidative markers in knee tissues of OA rats were mostly improved by the two therapeutic drugs. Such effect was also reflected in the rotarod, knee bend and knee swelling tests. Treatment with DIZE has shown a more prominent effect than LOS in controlling OA-associated inflammation and cellular oxidation. Markers of RAAS have also shown better responsiveness to DIZE over LOS. **Conclusions** DIZE has shown a prominent increase in the angiotensin 1–7 amount, highlighting the involvement of the signaling pathway in the immunomodulatory effect. The radiological and histopathology examination came to confirm the outcome of biochemical markers, nominating diminazene aceturate as a possible therapeutic option for OA.		
4.	Propolis-loaded nanostructured lipid carriers halt breast cancer progression through miRNA-223 related pathways: an in-vitro/in-vivo experiment	Oncology	The most frequent malignant tumor in women is breast cancer, and its incidence has been rising every year. Propolis has been used for its antibacterial, antifungal, and anti-inflammatory properties. The present study aimed to examine the effect of the Egyptian Propolis Extract (ProE) and its improved targeting using nanostructured lipid carriers (ProE-NLC) in Ehrlich Ascites Carcinoma (EAC) bearing mice, the common animal model for mammary tumors. EAC mice were treated either with 5-fluorouracil (5-FU), ProE, ProE-NLC, or a combination of ProE-NLC and 5-FU. Their effect on different inflammatory, angiogenic, proliferation and apoptotic markers,	2023	https://www.nature.com/articles/s41598-023-42709-7

			as well as miR-223, was examined. ProE and ProE-NLC have shown potential anti-breast cancer activity through multiple interrelated mechanisms including, the elevation of antioxidant levels, suppression of angiogenesis, inflammatory and mTOR pathways, and induction of the apoptotic pathway. All of which is a function of increased miRNA-223 expression. The efficiency of propolis was enhanced when loaded in nanostructured lipid carriers, increasing the effectiveness of the chemotherapeutic agent 5-FU. In conclusion, this study is the first to develop propolis-loaded NLC for breast cancer targeting and to recommend propolis as an antitumor agent against breast cancer or as an adjuvant treatment with chemotherapeutic agents to enhance their antitumor activity and decrease their side effects. Tumor targeting by ProE-NLC should be considered as a future therapeutic perspective in breast cancer.		
5.	Novel PEGylated cholephytosomes for targeting fisetin to breast cancer: in vitro appraisal and in vivo antitumoral studies	Oncology	Fisetin (FIS) is a multifunctional bioactive flavanol that has been recently exploited as anticancer drug against various cancers including breast cancer. However, its poor aqueous solubility has constrained its clinical application. In the current work, fisetin is complexed for the first time with soy phosphatidylcholine in the presence of cholesterol to form a novel biocompatible phytosomal system entitled "cholephytosomes." To improve fisetin antitumor activity against breast cancer, stearylamine bearing cationic cholephytosomes (mPHY) were prepared and furtherly modified with hyaluronic acid (HPHY) to allow their orientation to cancer cells through their surface exposed phosphatidylserine and CD-44 receptors, respectively. In vitro characterization studies revealed promising physicochemical	2023	https://link.springer.com/article/10.1007/s13346-023-01409-5

			properties of both modified vesicles (mPHY and HPHY) including excellent FIS complexation efficiency (˷100%), improved octanol/water solubility along with a sustained drug release over 24 h. In vitro cell line studies against MDA-MB-231 cell line showed about 10- and 3.5-fold inhibition in IC50 of modified vesicles compared with free drug and conventional drug-phospholipid complex, respectively. Preclinical studies revealed that both modified cholephytosomes (mPHY and HPHY) had comparable cytotoxicity that is significantly surpassing free drug cytotoxicity. TGF-β1and its non-canonical related signaling pathway; ERK1/2, NF-κB, and MMP-9 were involved in halting tumorigenesis. Thus, tailoring novel phytosomal nanosystems for FIS could open opportunity for its clinical utility against cancer.		
6.	Rhein methotrexate-decorated solid lipid nanoparticles altering adjuvant arthritis progression through endoplasmic reticulum stress-mediated apoptosis	Autoimmune Pharmacology	Methotrexate (MTX) and diacerein (DIA) are two of the most potent disease-modifying anti-rheumatic drugs used for the treatment of rheumatoid arthritis (RA). DIA has reflected some GIT and hepatobiliary manifestations in numerous cases. It undergoes biotransformation in the liver into the active metabolite rhein (RH) which is characterized by its excellent anti-inflammatory activity and lower side effects. However, RH's hydrophobic nature and low bioavailability do not encourage its use in RA. The current study aims to use RH in combination with MTX in targeted solid lipid nanoparticles (RH-MTX-SLNs) for better effectiveness and shadowing light on its possible mechanistic pathways. RH-MTX-SLNs were prepared and assessed for their quality attributes. The effect of the formulation was assessed in-vivo in an adjuvant arthritis animal model investigating the role of the endoplasmic reticulum stress (ERS)-induced apoptosis. Results revealed	2023	https://link.springer.com/article/10.1007/s10787-023-01295-w

			that RH-MTX-SLNs were in the suitable nanosized range with high negative zeta potential indicating good stability. In-vivo, RH-MTX-SLNs significantly improved all measured inflammatory and arthritic markers, confirmed by electron microscopy and histology examination of the joints. Besides, the formulation was able to alter the ERS-mediated apoptosis. In conclusion, RH-MTX-SLNs can represent a promising therapeutic approach for RA showing significant anti-arthritic activity.		
7.	Self-assembled Fisetin-phospholipid complex: fisetin-integrated phytosomes for effective delivery to breast cancer	Oncology	Nowadays, fisetin (FIS) is extensively studied as potent anticancer surrogate with a multitarget actions against various types of cancers including breast cancer. However, its poor aqueous solubility handicapped its clinical utility. The current work endeavored, for the first time, to develop FIS phytosomes (FIS-PHY) for improving its physicochemical properties and subsequently its anticancer activity. Optimization of FIS- phytosomes involved different preparation techniques (Thin film hydration and ethanol injection) and different FIS: phospholipid molar ratios (1:1, 1:2, and 1:3). Complex formation was confirmed by complexation efficiency, infrared spectroscopy (IR), solubility studies and transmission electron microscope. The optimized FIS-PHY of 1:1 M ratio (PHY1) exhibited a nanometric particle size of 233.01 ± 9.46 nm with homogenous distribution (PDI = 0.27), negative zeta potential of − 29.41 mV, 100% complexation efficiency and controlled drug release over 24 h. In-vitro cytotoxicity study showed 2.5-fold decrease in IC50 of PHY1 compared with free FIS. Also, pharmacodynamic studies confirmed the promoted cytotoxicity of PHY1 against breast cancer through	2023	https://www.sciencedirect.com/science/article/pii/S0939641123001625

			modulating TGF-β1/MMP-9 molecular pathways of tumorigenesis. Overall, overcoming FIS drawbacks were successfully achieved through development of innovative biocompatible phytosomal system.		
8.	The antidiabetic effect of superparamagnetic iron oxide nanoparticles highlights the role of WNT/AMPK/mTOR/FOXO1/mitochondrial DNA in muscle and kidney	Diabetes	Aim: To explore the antidiabetic effect of superparamagnetic iron oxide nanoparticles (SPIONs)-PEG-550 and its related metabolic pathways in muscles and kidney. Materials & methods: Diabetes was induced in 5-day neonatal rats; after confirming diabetes, treatment with SPIONs-PEG-550 started at different doses for 4 weeks. Routine analysis of glucose, insulin, adipocytokines, urea and creatinine was performed. The expression of several genes involved in metabolic pathways and the corresponding protein levels were examined. Results & conclusion: SPIONs-PEG-550 normalized the disturbed glucose homeostasis, reversed insulin resistance, adjusted the serum level of adipocytokines, and improved several disturbed downstream effectors of the insulin signaling and WNT pathway in both tissues. Histological examination of the muscle and pancreas has shown almost normal functional characteristics without remarkable adverse effects on the kidney.	2023	https://www.tandfonline.com/doi/abs/10.2217/nnm-2022-0136
9.	Creatine monohydrate for mitochondrial nutrition	Metabolism	Creatine monohydrate is the most widely used supplement form of Creatine (Cr). It is de novo synthesized from the amino acids: arginine, glycine, and methionine or supplied exogenously from red meat and fish. Tissues store Cr in both free and phosphorylated forms (Phosphocreatine, PCr). Cr and PCr, through the Phosphocreatine shuttle system, play an important role in the regulation and homeostasis of cellular energy metabolism especially in muscles and the central nervous system, where the mitochondria are key players in this	2023	https://www.sciencedirect.com/science/article/abs/pii/B9780323902564000047

			energy production machinery. This chapter will focus on the application of Cr monohydrate as a mitochondrial nutrient and an energy-boosting compound by increasing Cr/PCr stores. This results in improvement of physical performance, increased muscular strength, improved recovery after exercise, improved memory and neuronal activity. The application of Cr supplementation as a possible treatment for muscular, neurological, and neuromuscular diseases and its relation to the mitochondrial creatine kinase will be reviewed.		
10.	Novel bio-inspired lipid nanoparticles for improving the anti-tumoral efficacy of fisetin against breast cancer.	Oncology		2022	https://www.sciencedirect.com/science/article/abs/pii/S0378517322007384
11.	Pentoxifylline/Valsartan co-delivery in liposomal gel alters the inflammatory HMGB-1/TLR pathway and promotes faster healing in burn wounds: A promising	Pharmacology	Burn wounds are one of the most severe complex forms of trauma. Hence, new treatment strategies that facilitate the healing process; reduce the severity and the healing time is the main concern of the health care systems. In this work, pentoxifylline-valsartan, (PTX- VAL), loaded liposomes integrated into gel were designed for the first time as a novel co-delivery carrier for the treatment of burn wounds. The objective of this work was to investigate the ability of the nano-based liposomal system to co-entrap two repurposed drugs; hydrophilic pentoxifylline and lipophilic valsartan for topical treatment of burn wounds. The impact of increasing the phospholipid amount to enhance the co-entrapment of PTX and VAL was investigated and in-vitro evaluation of the	2022	https://www.sciencedirect.com/science/article/abs/pii/S0378517322006822

	repurposed approach.		prepared formulations was conducted to choose the optimum composition with the highest entrapment of both drugs adopting a simple, reliable derivative spectrophotometric method. Structure elucidation was also performed using a transmission electron microscope. In addition, A simple selected derivative spectrophotometric method was developed for the assay of PTX-VAL novel combination. The proven selectivity, precision and accuracy assured the reliability of this analytical method. Being economic and fast makes routine application of the developed analytical method is recommended in pharmaceutical industry. The selected liposomal formulation integrated into gel matrix (PTX-VAL-LG) showed; nanometric size, acceptable entrapment efficiency of both PTX and VAL as well as sustained release profiles and thus, enhanced action.		
12.	Role of Oxytocin in Different Neuropsychiatric, Neurodegenerative, and Neurodevelopmental Disorders.	Neuropharmacology	Oxytocin has recently gained significant attention because of its role in the pathophysiology and management of dominant neuropsychiatric disorders. Oxytocin, a peptide hormone synthesized in the hypothalamus, is released into different brain regions, acting as a neurotransmitter. Receptors for oxytocin are present in many areas of the brain, including the hypothalamus, amygdala, and nucleus accumbens, which have been involved in the pathophysiology of depression, anxiety, schizophrenia, autism, Alzheimer's disease, Parkinson's disease, and attention deficit hyperactivity disorder. Animal studies have spotlighted the role of oxytocin in social, behavioral, pair bonding, and mother–infant bonding. Furthermore, oxytocin protects fetal neurons against injury during childbirth and affects various behaviors, assuming its possible neuroprotective characteristics. In this review, we	2022	https://link.springer.com/chapter/10.1007/112_2022_72

			discuss some of the concepts and mechanisms related to the role of oxytocin in the pathophysiology and management of some neuropsychiatric, neurodegenerative, and neurodevelopmental disorders.		
13.	Intranasal Oxytocin Attenuates Cognitive Impairment, β-Amyloid Burden and Tau Deposition in Female Rats with Alzheimer's Disease: Interplay of ERK1/2/GSK3β/ Caspase-3	Neuropharmacology	Oxytocin is a neuropeptide hormone that plays an important role in social bonding and behavior. Recent studies indicate that oxytocin could be involved in the regulation of neurological disorders. However, its role in modulating cognition in Alzheimer's disease (AD) has never been explored. Hence, the present study aims to investigate the potential of chronic intranasal oxytocin in halting memory impairment & AD pathology in aluminum chloride-induced AD in female rats. Morris water maze was used to assess cognitive dysfunction in two-time points throughout the treatment period. In addition, neuroprotective effects of oxytocin were examined by assessing hippocampal acetylcholinesterase activity, β-amyloid 1–42 protein, and Tau levels. In addition, ERK1/2, GSK3β, and caspase-3 levels were assessed as chief neurobiochemical mediators in AD. Hippocampi histopathological changes were also evaluated. These findings were compared to the standard drug galantamine alone and combined with oxytocin. Results showed that oxytocin restored cognitive functions and improved animals' behavior in the Morris test. This was accompanied by a significant decline in acetylcholinesterase activity, 1–42 β-amyloid and Tau proteins levels. Hippocampal ERK1/2 and GSK3β were also reduced, exceeding galantamine effects, thus attenuating AD pathological hallmarks formation. Determination of caspase-3 revealed low cytoplasmic positivity, indicating the ceasing of neuronal	2022	https://link.springer.com/article/10.1007/s11064-022-03624-x

			death. Histopathological examination confirmed these findings, showing restored hippocampal cells structure. Combined galantamine and oxytocin treatment showed even better biochemical and histopathological profiles. It can be thus concluded that oxytocin possesses promising neuroprotective potential in AD mediated via restoring cognition and suppressing β-amyloid, Tau accumulation, and neuronal death.		
14.	Pectin coated nanostructured lipid carriers for targeted piperine delivery to hepatocellular carcinoma	Oncology	Piperine (PIP) is a herbal drug with well-known anticancer activity against different types of cancer including hepatocellular carcinoma. However, low aqueous solubility and extensive first-pass metabolism limit its clinical use. In this study, positively charged PIP-loaded nanostructured lipid carriers (PIP-NLCs) were prepared via melt-emulsification and ultra-sonication method followed by pectin coating to get novel pectin-coated NLCs (PIP-P-NLCs) targeting hepatocellular carcinoma. Complete in vitro characterization was performed. In addition, cytotoxicity and cellular uptake of nanosystems in HepG2 cells were evaluated. Finally, in vivo anticancer activity was tested in the diethylnitrosamine-induced hepatocellular carcinoma mice model. Successful pectin coating was confirmed by an increased particle size of PIP-NLCs from 150.28 ± 2.51 nm to 205.24 ± 5.13 nm and revered Zeta potential from 33.34 ± 3.52 mV to −27.63 ± 2.05 mV. Nanosystems had high entrapment efficiency, good stability, spherical shape, and sustained drug release over 24 h. Targeted P-NLCs enhanced the cytotoxicity and cellular uptake compared to untargeted NLCs. Furthermore, PIP-P-NLCs improved in vivo anticancer effect of PIP as proved by histological examination of liver tissues, suppression of liver	2022	https://www.sciencedirect.com/science/article/abs/pii/S0378517322002678

			enzymes and oxidative stress environment in the liver, and alteration of cell cycle regulators. To conclude, PIP-P-NLCs can act as a promising approach for targeted delivery of PIP to hepatocellular carcinoma.		
15.	The α7 nAChR allosteric modulator PNU-120596 amends neuroinflammatory and motor consequences of parkinsonism in rats: Role of JAK2/NF-κB/GSk3β/TNF-α pathway	Neuropharmacology	Parkinson's disease (PD) is the second most common neurodegenerative disorder and a leading cause of disability. The current gold standard for PD treatment, L-Dopa, has limited clinical efficacy and multiple side effects. Evidence suggests that activation of α7 nicotinic acetylcholine receptors (α7nAChRs) abrogates neuronal and inflammatory insults. Here we tested whether PNU-120596 (PNU), a type II positive allosteric modulator of α7 nAChR, has a critical role in regulating motor dysfunction and neuroinflammation correlated with the associated PD dysfunction. Neuroprotective mechanisms were investigated through neurobehavioral, molecular, histopathological, and immunohistochemical studies. PNU reversed motor incoordination and hypokinesia induced via the intrastriatal injection of 6-hydroxydopamine and manifested by lower falling latency in the rotarod test, short ambulation time and low rearing incidence in open field test. Tyrosine hydroxylase immunostaining showed a significant restoration of dopaminergic neurons following PNU treatment, in addition to histopathological restoration in nigrostriatal tissues. PNU halted striatal neuroinflammation manifested as a suppressed expression of JAK2/NF-κB/GSk3β accompanied by a parallel decline in the protein expression of TNF-α in nigrostriatal tissue denoting the modulator anti-inflammatory capacity. Moreover, the protective effects of PNU were partially reversed by the α7 nAChR antagonist, methyllycaconitine,	2022	https://www.sciencedirect.com/science/article/pii/S0753332222001640

			indicating the role of α7 nAChR modulation in the mechanism of action of PNU. This is the first study to reveal the positive effects of PNU-120596 on motor derangements of PD via JAK2/NF-κB/GSk3β/ TNF-α neuroinflammatory pathways, which could offer a potential therapeutic strategy for PD.		
16.	Does physical exercise improve or deteriorate treatment of multiple sclerosis with mitoxantrone? Experimental autoimmune encephalomyelitis study in rats	Autoimmune Pharmacology	Background Mitoxantrone has proved efficacy in treatment of multiple sclerosis (MS). The fact that physical exercise could slow down the progression of disease and improve performance is still a debatable issue, hence; we aimed at studying whether combining mitoxantrone with exercise is of value in the management of MS. Methods Thirty-six male rats were divided into sedentary and exercised groups. During a 14-day habituation period rats were subjected to exercise training on a rotarod (30 min/day) before Experimental Autoimmune Encephalomyelitis (EAE) induction and thereafter for 17 consecutive days. On day 13 after induction, EAE groups (exercised &sedentary) were divided into untreated and mitoxantrone treated ones. Disease development was evaluated by motor performance and EAE score. Cerebrospinal fluid (CSF) was used for biochemical analysis. Brain stem and cerebellum were examined histopathological and immunohistochemically. Results Exercise training alone did not add a significant value to the studied parameters, except for reducing Foxp3 immunoreactivity in EAE group and caspase-3 in the mitoxantrone treated group. Unexpectedly, exercise worsened the mitoxantrone effect on EAE score, Bcl2 and Bax.	2022	https://bmcneurosci.biomedcentral.com/articles/10.1186/s12868-022-00692-1

			Mitoxantrone alone decreased EAE/demyelination/inflammation scores, Foxp3 immunoreactivity, and interleukin-6, while increased the re-myelination marker BDNF without any change in tumor necrosis factor-α. It clearly interrupted the apoptotic pathway in brain stem, but worsened EAE mediated changes of the anti-apoptotic Bcl2 and pro-apoptotic marker Bax in the CSF. Conclusions The neuroprotective effect of mitoxantrone was related with remyelination, immunosuppressive and anti-inflammatory potentials. Exercise training did not show added value to mitoxantrone, in contrast, it disrupts the apoptotic pathway.		
17.	Modulation by antenatal therapies of cardiovascular and renal programming in male and female offspring of preeclamptic rats	Pharmacology	Morbidity and mortality risks are enhanced in preeclamptic (PE) mothers and their offspring. Here, we asked if sexual dimorphism exists in (i) cardiovascular and renal damage evolved in offspring of PE mothers, and (ii) offspring responsiveness to antenatal therapies. PE was induced by administering NG-nitro-L-arginine methyl ester (L-NAME, 50 mg/kg/day, oral gavage) to pregnant rats for 7 days starting from gestational day 14. Three therapies were co-administered orally with L-NAME, atrasentan (endothelin ETA receptor antagonist), terutroban (thromboxane A2 receptor antagonist, TXA2), or α-methyldopa (α-MD, central sympatholytic drug). Cardiovascular and renal profiles were assessed in 3-month-old offspring. Compared with offspring of non-PE rats, PE offspring exhibited elevated systolic blood pressure and proteinuria and reduced heart rate and creatinine clearance (CrCl). Apart from a greater bradycardia in male offspring, similar PE effects were noted in male and female offspring. While terutroban, atrasentan, or α-MD partially and similarly	2021	https://link.springer.com/article/10.1007/s00210-021-02146-7

			blunted the PE-evoked changes in CrCl and proteinuria, terutroban was the only drug that virtually abolished PE hypertension. Rises in cardiorenal inflammatory (tumor necrosis factor alpha, TNFα) and oxidative (isoprostane) markers were mostly and equally eliminated by all therapies in the two sexes, except for a greater dampening action of atrasentan, compared with α-MD, on tissue TNFα in female offspring only. Histopathologically, antenatal terutroban or atrasentan was more effective than α-MD in rectifying cardiac structural damage, myofiber separation, and cytoplasmic alterations, in PE offspring. The repair by antenatal terutroban or atrasentan of cardiovascular and renal anomalies in PE offspring is mostly sex-independent and surpasses the protection offered by α-MD, the conventional PE therapy.		
18.	Prenatal endothelin or thromboxane receptor antagonism surpasses sympathoinhibition in improving cardiorenal malfunctions in preeclamptic rats	Pharmacology	Current therapies for preeclampsia (PE) and its complications are limited and defective. Considering the importance of endothelin (ET) and thromboxane A2 (TXA2) signaling in PE pathophysiology, we tested the hypothesis that prenatal blockade of endothelin ETA or thromboxane TXA2 receptors favorably reprograms preeclamptic cardiovascular and renal insults. PE was induced by daily oral administration of L-NAME (50 mg/kg) to pregnant rats for 7 consecutive days starting from gestational day 14. The effects of co-exposure to atrasentan (ETA receptor blocker, 10 mg/kg/day) or terutroban (TXA2 receptor blocker, 10 mg/kg/day) on cardiovascular and renal anomalies induced by PE were assessed on gestational day 20 (GD20) and at weaning time and compared with those evoked by the sympatholytic drug α-methyldopa (α-MD, 100 mg/kg/day), a prototypic therapy for PE management. Among all drugs, terutroban was basically the most potent in	2021	https://www.sciencedirect.com/science/article/abs/pii/S0041008X21002192

			ameliorating PE-evoked increments in blood pressure and decrements in creatinine clearance. Cardiorenal tissues of PE rats exhibited significant increases in ETA and TXA2 receptor expressions and these effects disappeared after treatment with atrasentan and to a lesser extent by terutroban or α-MD. Atrasentan was also the most effective in reversing the reduced ETB receptor expression in renal tissues of PE rats. Signs of histopathological damage in cardiac and renal tissues of PE rats were mostly improved by all therapies. Together, pharmacologic elimination of ETA or TXA2 receptors offers a relatively better prospect than α-MD in controlling perinatal cardiorenal irregularities sparked by PE.		
19.	The effective interplay of (non-) selective NSAIDs with neostigmine in animal models of analgesia and inflammation.	Pharmacology	Background Surgical procedures cause perioperative immunosuppression and neuroendocrine stress, exerted by activation of the autonomic nervous system and the hypothalamic-pituitary-adrenal axis. The acetylcholinesterase inhibitor (ACHEI); neostigmine, is known clinically for its analgesic effect in the perioperative phases proving high efficacy; besides possessing anti-inflammatory properties controlling immune cells and cytokine level. Hence, this study evaluated and compared the analgesic and anti-inflammatory activities of the combination of selective Cox-2 inhibitor; celecoxib, with neostigmine versus a combination of the non-selective Cox inhibitor; diclofenac, with neostigmine; in different experimental models of analgesia and inflammation in rats. Methods Analgesic activity of neostigmine with/without diclofenac or celecoxib was assessed in female Sprague-Dawely rats using the tail clip model and acetic acid induced writhing. Serum	2021	https://link.springer.com/article/10.1186/s40360-021-00488-9

			level of β-endorphin was assessed after the tail clip test. The anti-inflammatory activity was evaluated using acute and sub-chronic formalin induced paw edema. At the end of the sub-chronic formalin test, blood samples were collected for analysis of anti-inflammatory, liver and kidney function markers. Livers, kidneys and hind paws were also examined histopathologically. Results Addition of neostigmine to selective or non-selective NSAIDs (celecoxib or diclofenac) causes an increased level of analgesia of NSAIDs with rapid onset of action and short duration, while causing potentiation of the anti-inflammatory effect of neostigmine as seen in the tail clip, writhing, formalin test, Cox-1 and Cox-2 activities, serum β-endorphin, TNF-α, NF-κB and HS-CRP. All combinations of this study disturb some kidney and liver functions, however with normal histopathological appearances, while hind paws reveal improved inflammatory infiltration in all treated groups. Conclusions Selective and non-selective NSAIDs examined in this study could be good adjunct options to general anesthetic agents and neostigmine in perioperative stages, an outcome that needs further clinical investigations.		
20.	Galantamine nanoparticles outperform oral galantamine in an Alzheimer's rat model: pharmacokinetic	Neuropharmacology	Aim: Galantamine is an acetylcholinesterase inhibitor frequently used in Alzheimer's disease management. Its cholinergic adverse effects and rapid elimination limit its therapeutic outcomes. We investigated the pharmacodynamics and pharmacokinetics of 2-week intranasal galantamine-bound chitosan nanoparticles (G-NP) treatment in scopolamine-induced Alzheimer's disease rat model. Materials & methods:	2021	https://www.futuremedicine.com/doi/abs/10.2217/nnm-2021-0051

	s and pharmacodynamics.		Behavioral, neurobiochemical and histopathological changes were assessed and compared with oral and nasal solutions. Brain uptake and pharmacokinetics were determined using a novel validated LC/MS assay. Results: G-NP enhanced spatial memory, exploring behavior and cholinergic transmission in rats. Beta-amyloid deposition and Notch signaling were suppressed and the histopathological degeneration was restored. G-NP potentiated galantamine brain delivery and delayed its elimination. Conclusion: G-NP hold promising therapeutic potentials and brain targeting, outperforming conventional galantamine therapy.		
21.	Oral Genistein-loaded Phytosomes with Enhanced Hepatic Uptake, Residence and Improved Therapeutic Efficacy against Hepatocellular Carcinoma.	Oncology	Genistein (Gen) is one of the most potent soy isoflavones used for hepatocellular carcinoma (HCC) treatment. Low aqueous solubility and first-pass metabolism are the main obstacles resulting in low Gen oral bioavailability. The current study aims to introduce phytosomes as an approach to improve Gen solubility, protect it from metabolism by complexation with phospholipids (PL), and get used to PL in Gen lymphatic delivery. Different forms of PL namely: Lipiod® S100, Phosal® 53 MCT, and Phosal®75 SA were used in phytosomes preparation GP, GPM, and GPL respectively. The effect of formulation components on Gen absorption, metabolism, and liver accumulation was evaluated following oral administration to rats. Cytotoxicity and cellular uptake studies were applied on HepG2 cells and in-vivo anti-tumor studies were applied to the DEN-mice model. Results revealed that GP and GPL remarkably accumulated Gen aglycone in hepatic cells and minimized the metabolic effect on Gen. They significantly increased the intracellular accumulation of Gen in its complex form in HepG2 cells. Their cytotoxicity is time-	2021	https://www.sciencedirect.com/science/article/abs/pii/S0378517321003690

			dependent according to the complex stability. The enhanced in-vivo anti-tumor effect was observed for GP and GPL compared to Gen suspension on DEN-induced HCC in mice. In conclusion, Gen-phytosomes can represent a promising approach for liver cancer treatment.		
22.	Neuroprotective role of galantamine with/without physical exercise in experimental autoimmune encephalomyelitis in rats.	Autoimmune Pharmacology	Aims The fact that physical activity besides central cholinergic enhancement contributes in improving neuronal function and spastic plasticity, recommends the use of the anticholinesterase and cholinergic drug galantamine with/without exercise in the management of the experimental autoimmune encephalomyelitis (EAE) model of multiple sclerosis (MS). Materials and methods Sedentary and 14 days exercised male Sprague Dawley rats were subjected to EAE. Hereafter, exercised rats continued on rotarod for 30 min for 17 consecutive days. At the onset of symptoms (day 13), EAE sedentary/exercised groups were subdivided into untreated and post-treated with galantamine. The disease progression was assessed by EAE score, motor performance, and biochemically using cerebrospinal fluid (CSF). Cerebellum and brain stem samples were used for histopathology and immunohistochemistry analysis. Key findings Galantamine decreased EAE score of sedentary/exercised rats and enhanced their motor performance. Galantamine with/without exercise inhibited CSF levels of tumor necrosis factor (TNF)-α, interleukin (IL)-6), and Bcl-2-associated X protein (Bax), besides caspase-3 and forkhead box P3 (Foxp3) expression in the brain stem. Contrariwise, it has elevated CSF levels of brain derived neurotrophic factor (BDNF) and B-cell	2021	https://www.sciencedirect.com/science/article/abs/pii/S0024320521004446

			lymphoma (Bcl-2) and enhanced remyelination of cerebral neurons. Noteworthy, exercise boosted the drug effect on Bcl-2 and Bax. Significance The neuroprotective effect of galantamine against EAE was associated with anti-inflammatory and anti-apoptotic potentials, along with increasing BDNF and remyelination. It also normalized regulatory T-cells levels in the brain stem. The impact of the add-on of exercise was markedly manifested in reducing neuronal apoptosis.		
23.	Valsartan Solid Lipid Nanoparticles Integrated Hydrogel: A Challenging repurposed use in the treatment of diabetic foot ulcer, In-vitro/In-vivo Experimental study.	Diabetes	The article presents an experimental study on the possible repurposed use of valsartan (Val), in the local treatment of uncontrolled diabetic foot ulcer. Solid lipid nanoparticles (SLN), loaded with Val were prepared by applying 32 full factorial design using modified high shear homogenization method. The lipid phase composed of Precirol® ATO 5 (P ATO 5) and/or Gelucire 50/13 (G 50/13) in different ratios and a nonionic emulsifier, Pluronic 188 (P188), was used in different percentages. Optimized formulation was further integrated in hydroxyl propyl methyl cellulose (HPMC) gel for the ease of administration. In-vitro and in-vivo characterizations were investigated. The prepared nanoparticles showed small particle size, high entrapment efficiency and sustained drug release. Microbiologically, Val-SLN showed a prominent decrease in the biofilm mass formation for both gram-positive and gram-negative bacteria, as well as a comparable minimum inhibitory concentration level to levofloxacin alone. Diabetes was induced in 32 neonatal Sprague-Dawley rats. At 8 weeks of age, rats with blood sugar level >160 were subjected to surgically induced	2021	https://www.sciencedirect.com/science/article/abs/pii/S0378517320310760

			ulcer. Treatment with Val-SLN for 12 days revealed enhanced healing characteristics through cyclooxygenase-2 (COX-2), nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), nitric oxide (NO), transforming growth factor-beta (TGF-β), matrix metalloproteinase (MMPs) and vascular endothelial growth factor (VEGF) pathways. Histological examination revealed re-epithelization in Val-SLN treated ulcer, as well as decrease in collagen using trichrome histomorphometric analysis.		
24.	Polymyxin B prevents the development of adjuvant arthritis via modulation of TLR/Cox-2 signaling pathway.	Autoimmune Pharmacology	Aims Several microbial toll-like receptor (TLR) ligands, bacterial DNA and bacterial cell wall fragments have been identified in the synovium of rheumatoid arthritis (RA) patients, proving bacterial involvement in the pathogenesis of RA. The current study aimed to verify that low dose polymyxin B could prevent the development of chronic inflammatory arthritis. Methods Twelve days post adjuvant injection, Sprague-Dawley rats were treated twice weekly with methotrexate (0.5 mg/kg) or daily with polymyxin B (1 mg/kg) or with combination of both for 1 or 2 weeks. Arthritis progression was assessed by hind paw swelling, serum levels of tumor growth factor-1β (TGF-1β), tumor necrosis factor-alpha (TNF-α), high sensitivity C-reactive protein (HS-CRP) and nuclear factor kappa B (NF-κB) were measured using ELISA. Cyclooxygenase-1 (Cox-1) and Cox-2 activities, as well as mRNA expression of TLR-2 and TLR-4 were determined. Histopathological examination of the ankle joint was performed as well as immunohistochemistry for anti-TLR-4. Histopathological assessment of toxic effects on the kidney was performed.	2020	https://www.sciencedirect.com/science/article/abs/pii/S002432052031002X

			Key findings Adjuvant arthritis led to a significant swelling of the hind paw and alteration in all serum parameters, TLR-2 and TLR-4 expression, as well as Cox-2 activity. These alterations were associated with histopathological changes of the joints. Polymyxin B reduced significantly all biomarkers of inflammation, showing better effect of the combination in most of the studied parameters, with minimal signs of nephrotoxicity. Significance In conclusion, results showed that polymyxin B possesses significant anti-arthritic activity which may be attributed to inhibition of the TLR-4, NF-κB and Cox-2 signaling pathway.		
25.	Galantamine in rheumatoid arthritis: A cross talk of parasympathetic and sympathetic system regulates synovium-derived microRNAs and related pathogenic pathways.	Autoimmune Pharmacology	The acetylcholinesterase inhibitor, galantamine, has shown therapeutic effect in rat model of rheumatoid arthritis. Hence, the current study aims at determining the mode of action of galantamine by examining different synovium-derived microRNAs (miRs) and their related pathogenic pathways. The study also focuses on how parasympathetic and sympathetic pathways in the synovial tissue could affect the mode of action and anti-arthritic effect of galantamine. Chemical sympathectomy was initiated in 12 adjuvant arthritic rats by exposure to 6-hydroxydopamine (6-OHDA; 2 × 50 mg/kg) on day 9 after adjuvant injection and again (2 × 100 mg/kg) one week later. Six rats were treated with galantamine (2.5 mg/kg/day) to explore the influence of sympathetic impairment on galantamine effect. Another twelve additional adjuvant arthritic rats were exposed to the selective α7 nicotinic acetylcholine receptor blocker methylcaconitine	2020	https://www.sciencedirect.com/science/article/abs/pii/S0014299920304076

			citrate (MLA; 5.6 mg/kg/day), 15 min before galantamine treatment. As control, six adjuvant arthritic rats were treated with galantamine alone. Treatment proceeded for 5 days, from day 14 till day 18 post-adjuvant injection. Different miRs and their related pathogenic pathways were examined. Tyrosine hydroxylase (TH) expression was also measured in joint tissue. Galantamine affected the expression of the different miRs and their related parameters. Both, 6-OHDA and MLA, interrupted the anti-inflammatory/anti-arthritic effect of galantamine to different extent. Additionally, TH expression in the synovium was affected by galantamine, suggesting a novel pathogenic target in the treatment of rheumatoid arthritis.		
26.	Enhanced mitochondrial biogenesis is involved in the ameliorative action of creatine supplementation in rat's soleus and cardiac muscles.	Metabolism	The current study focused on the effect of creatine supplementation with/without exercise on the expression of genes controlling mitochondrial biogenesis in skeletal and cardiac muscles, as well as its safety profile on the liver and kidney. A total of 40 male Wister rats were included in the present study. Two unexercised groups: The control sedentary group and the sedentary creatine-treated group (n=10) were treated daily with oral creatine (0.5 g/kg per day). Two exercised groups performed swimming exercise training 5 days/week for a period of 5 weeks; The Exercise training group, and exercise training and creatine (0.5 g/kg per day) treated group. After sacrifice, blood samples, cardiac and soleus muscles were collected for assessment of mtDNA copy number, gene expression analysis and nuclear extraction for the assay of PGC-1α. The results of the current study demonstrated that, physical activity with short-term creatine supplementation increased all factors of mitochondrial biogenesis, an effect that is devoid of any kidney or liver	2020	https://www.spandidos-publications.com/10.3892/etm.2019.8173

			adverse effects. Further studies are still required to explore the potential of creatine supplementation in ameliorating mitochondrial diseases, including epilepsy, skeletal and cardiac myopathies, hepatopathies and nephropathies.		
27.	The role of α7nAChR in controlling the anti-inflammatory/anti-arthritic action of Galantamine.	Autoimmune Pharmacology	Objective The evolution of the "cholinergic anti-inflammatory pathway" and the fact that the α 7 subunit of the nicotinic acetylcholine receptor (α7nAChR) is present in the spleen, joint and on the surface of lymphocytes, opened up the prospective in this study of targeting the α7nAChR by the anticholinesterase and cholinergic drug, galantamine, to control inflammation in rheumatoid arthritis (RA). Methods Twelve-adjuvant arthritic rats were exposed to the selective α7nAChR blocker methylcaconitine citrate 15 min before galantamine treatment. As control, six adjuvant arthritic rats were treated with galantamine and six others were untreated. After five days TNF-α levels were assessed in spleen and joints, while reduced glutathione was measured in blood and joint tissue. In the second part, magnetically sorted CD4 + T cells from peripheral blood mononuclear cells of RA patients and healthy donors were used to sort CD4 + CD25 – primary T cells (Tresp) and CD4 + CD25 + CD127low Tregs. The suppressive function of Tregs was investigated after incubation with galantamine using flow cytometry. Cell culture supernatants were analyzed for TNF-α and IL-10 levels after three days incubation period of Tregs with Tresp. The effect of galantamine on Tregs was then blocked by α-Bungarotoxin and the same assay has been repeated. Results & conclusion	2019	https://www.sciencedirect.com/science/article/abs/pii/S0006295219303648

			Selective α7nAChR blockade interrupted the anti-inflammatory effect of galantamine in the spleen and joints of arthritic rats. In healthy donors, galantamine could strengthen the suppressive activity of Tregs; while in RA patients it did not modulate the function of Tregs significantly. Further studies are necessary to investigate whether modulation of the cholinergic nervous system, especially α7nAChR, could have impact on the disturbed immune system in RA, which may open up a new treatment option of autoimmune diseases.		
28.	Controlled release Ibu-cryobarriers for the prevention of post-operative adhesions: In-vitro/in-vivo comparative study.	Pharmacology	Post-operative adhesion is a common cause of several complications including intestinal obstruction, chronic pelvic pain and/or infertility. Adhesions are fibrous bands that result from the inflammatory reactions due to peritoneum damage. The current study focused on designing an effective anti-inflammatory loaded barrier for the prevention of post-operative adhesions. The proposed method is based on the use of polyvinyl alcohol (PVA), cryobarrier loaded with Ibuprofen (Ibu). Anti-adhesive Ibu-cryobarriers were prepared in different forms, and subjected to in-vitro evaluation comprising; drug release rate, maximum swelling index, morphological examination using scanning electron microscope (SEM), fourier-transform infrared spectroscopy (FTIR) and mechanical properties. Optimized cryobarriers were further investigated for their in-vivo effectiveness in preventing post-operative adhesions in female Sprague-Dawley rats. All formulations showed appropriate physical and morphological characteristics, in-vitro controlled sustained drug release profiles during a period of seven days with acceptable maximum swelling index. Invivo, all cryobarriers were equivalent to each other concerning serum or tissue	2019	https://www.sciencedirect.com/science/article/abs/pii/S0378517319303527

			parameter. However, morphological and histopathological evaluations revealed that both xerocryogel and lyophilized cryofilms are more effective than the cryogel in prevention of post-operative peritoneal adhesions. The current study showed the possibility of preparing drug loaded cryobarriers using simple technique with an effective in vivo post-operative adhesion prevention.		
29.	Effect of galantamine on adjuvant-induced arthritis in rats	Autoimmune Pharmacology	Stimulation of the vagus nerve suppresses cytokine production and macrophage activation, via the interaction of its neurotransmitter acetylcholine (ACh) with the α7 subunit of the nicotinic acetylcholine receptor (α7nAChR), present on neurons and inflammatory cells. The present study aimed to verify the potential anti-inflammatory effect of galantamine against experimental arthritis induced in rats. Fourteen days post adjuvant injection, Sprague-Dawley rats were treated orally with three doses of galantamine (1.25, 2.5 and 5 mg/kg) or leflunomide (10 mg/kg) for 2 weeks and arthritis progression was assessed by hind paw swelling. Additionally, serum biomarkers, viz., anti-cyclic citrullinated peptide antibodies (Anti-CCP), tumor necrosis factor-α (TNF-α), interleukin-10 (IL-10) and monocyte chemoattractant protein-1 (MCP-1) were measured. Radiological examination of the hind paws was also carried out to evaluate the degree of joint damage. Adjuvant arthritis led to a significant weight loss, marked swelling of the hind paw and alteration in the serum levels of anti-CCP, TNF-α, IL-10 and MCP-1. These alterations were associated with significant radiological changes of the joints. Galantamine, in a dose-dependent manner, reduced significantly all biomarkers of inflammation, with the highest	2015	https://www.sciencedirect.com/science/article/pii/S0014299915301643

			dose showing the best beneficial anti-inflammatory effect that was superior in magnitude to the reference drug leflunomide in most of the studied parameters. In conclusion, these results suggest that galantamine may represent a novel, inexpensive and effective therapeutic strategy in the treatment of rheumatoid arthritis.		
30.	A New Approach in Rheumatoid Arthritis.	Autoimmune Pharmacology	Rheumatoid arthritis (RA) is a systemic autoimmune disease characterized by chronic inflammation of the synovial joints, ultimately leading to a progressive and irreversible joint destruction. Early diagnosis and treatment of rheumatoid arthritis reduce joint destruction, preserve function, and improve survival. Therefore, critical issues concerning the effect of therapy are to control symptoms and signs of the disease for prolonged periods, as well as the capacity to retard the damaging effect of inflammation on articular cartilage and bone. No single agent is completely effective in treating disease pathology and is devoid of side effects; consequently, a safe and effective treatment for RA remains elusive and additional therapies, with novel mechanisms of action, are therefore needed .	2013	https://www.morebooks.de/store/gb/book/a-new-approach-in-rheumatoid-arthritis/isbn/978-3-659-45124-9
31.	Evaluation of the effect of losartan and methotrexate combined therapy in adjuvant-induced arthritis in rats	Autoimmune Pharmacology	There is increasing body of evidence documenting the involvement of Angiotensin II (Ang II) in inflammatory diseases. Moreover the up-regulation of Ang II type 1 (AT1) receptors in synovium of rheumatoid arthritis (RA) patients has been previously described. Objectives: To investigate the anti-inflammatory effect of losartan, the selective AT1 receptor blocker, and to compare the efficacy of methotrexate (MTX) alone and in combination with losartan in adjuvant arthritis (AA) in rats.	2013	https://www.sciencedirect.com/science/article/pii/S0014299912008928?v=s5

			Methods: Twelve days post adjuvant injection, Sprague-Dawley rats were treated with MTX (1mg/kg/week), losartan (20 mg/kg/day) and their combination for 15 days. Severity of arthritis was assessed by hind paw swelling, arthrogram scores. Serum was analyzed for measurement of albumin, C-reactive protein (CRP), nitrite/nitrate concentrations, interleukin 1β (IL-1β), tumor necrosis factor-α (TNF-α), vascular endothelial growth factor (VEGF), aspartate transaminase (AST) and alanine transaminase (ALT). Histopathological examination was done for hind paws and livers. Results: MTX and losartan monotherapies significantly reduced all parameters of inflammation and arthritis with better results in the MTX group except for the transaminases where losartan caused more significant reduction in their serum levels. The combined therapy showed better results than MTX and losartan alone. Hind paws showed better improvement of inflammatory cell infiltration and bone resorption in the combined therapy group. Disturbances in liver architecture, fibrosis and granulomata caused by AA were reverted to normal status in the combined therapy group in contrast to losartan and MTX monotherapies. In conclusion, MTX and losartan combined therapy provided more effective anti-inflammatory and hepatoprotective effects than either drug alone.		