Publications Template

#	Research Title	Field	Abstract	Year of Publication	Publishing Link "URL"
1	Evaluation of the anticarcinogenic effect of some peroxisome proliferator activated receptor ligands on dimethylbenz (α) anthracene induced mammary tumor in female rats	Pharmacology & Pharmacy	Introduction: Breast cancer is the leading cause of cancer death among females worldwide. Peroxisome proliferator activated receptors (PPARs) are one of several nuclear receptors involved in the biology of breast cancer. Aim: Compare the effect of fenofibrate (PPARα ligand), pioglitazone (PPAR γ ligand) and omega-3 (PPARα, γ ligand) and their probable mechanisms of action on 7, 12 dimethylbenz (α) anthracene (DMBA)-induced mammary carcinoma in female rats. Methods: Fifty female Waister albino rats were utilized, with ten serving as plain controls. The remaining were subjected to induction of mammary carcinomas by oral intubation with a single dose of 20 mg DMBA suspended in one ml of sesame oil. After the appearance of mammary tumors, rats were randomly assigned to 4 orally-treated groups: untreated, fenofibrate, pioglitazone and omega-3-treated for 28 days. Assessed parameters: Percentage change of tumor volume, serum and tumor tissue vascular endothelial growth factor levels, tumor caspase-3 and cyclooxygenase-2 concentrations, as well as immunohistochemical detection of Ki-67 expression. Results: The untreated rats had progressive increase in mammary tumor volume. Treatment with fenofibrate, pioglitazone or omega-3 significantly reduced the rate of tumor growth via antiangiogenic, proapoptotic, antiproliferative and anti-inflammatory effects. Conclusion: Fenofibrate, pioglitazone and omega-3 exerted anti-tumor effects on breast cancer induced in rats via numerous mechanisms of action.	2015	https://scholar.google.com.eg/citations?view_op=view_citation&hl=en&user=BjQdQEYAAAAJ&citation_for_view=BjQdQEYAAAAJ:UeHWp8X0CEIC

2	Hepatic stellate cell-targeted imatinib nanomedicine versus conventional imatinib: a novel strategy with potent efficacy in experimental liver fibrosis	Pharmacology & Pharmacy	Liver fibrosis is a global health problem without approved treatment. Imatinib inhibits two key profibrotic pathways; platelet-derived growth factor (PDGF) and transforming growth factor-beta (TGF-β) and thus can be used to treat liver fibrosis. However, conventional imatinib therapy is hampered by low concentration at target tissue and increased toxicity to other tissues especially heart, lung and liver. Since hepatic stellate cells (HSCs) are the main contributors to liver fibrosis pathogenesis and sole hepatic vitamin A (V_A) storage cells, they can be actively targeted by coupling liposomes to V_A. In this study, novel V_A-coupled imatinib-loaded liposomes (ILC) were prepared and optimized regarding V_A-coupling efficiency, imatinib entrapment efficiency, and particle size. Preferential accumulation of the selected formula in liver was proved by tracing intraperitoneally (i.p.)-injected V_A-coupled liposomes loaded with Nile Red (LCNR) to rats with CCl_4-induced liver fibrosis using live animal imaging. Co-localization of LCNR with immunofluorescently-labeled PDGFR-β in frozen liver tissue sections confirmed HSCs targeting. ILC bio-distribution, following single i.p. injection, revealed 13.5 folds higher hepatic accumulation than conventional imatinib in addition to limited bio-distribution to other organs including heart and lung reflecting diminished adverse effects. ILC therapy resulted in a potent inhibition of phosphorylated PDGFR-β expression when compared to conventional imatinib. Subsequently, there was a statistically significant improvement in liver function tests and reversal of hepatotoxicity along with liver fibrosis. Anti-fibrotic effect was evident from histopathologic Ishak score reduction as well as normalization of the level of profibrotic mediators (hydroxyproline, TGF-B and matrix metalloproteinase-2). Thus, HSC-targeted imatinib therapy shows outstanding anti-fibrotic effects with reduced cytotoxicity compared to conventional imatinib. It can represent a promising novel approach for liver fibrosis treatment.	2017	https://www.sciencedirect.com/science/article/abs/pii/S0168365917308696

3	Oral vitamin-A-coupled valsartan nanomedicine: High hepatic stellate cell receptors accessibility and prolonged enterohepatic residence	Pharmacology & Pharmacy	So far, liver fibrosis still has no clinically-approved treatment. The loss of stored vitamin-A (V_A) in hepatic stellate cells (HSCs), the main regulators to hepatic fibrosis, can be applied as a mechanism for their targeting. Valsartan is a good candidate for this approach; it is a marketed oral-therapy with inverse- and partial-agonistic activity to the over-expressed angiotensin-II type1 receptor (AT1R) and depleted nuclear peroxisome proliferator-activated receptor-gamma (PPAR-γ), respectively, in activated HSCs. However, efficacy on AT1R and PPAR-γ necessitates high drug permeability which is lacking in valsartan. In the current study, liposomes were used as nanocarriers for valsartan to improve its permeability and hence efficacy. They were coupled to V_A and characterized for HSCs-targeting. Tracing of orally-administered fluorescently-labeled V_A-coupled liposomes in normal rats and their fluorescence intensity quantification in different organs convincingly demonstrated their intestinal entrapment. On the other hands, their administration to rats with induced fibrosis revealed preferential hepatic, and less intestinal, accumulation which lasted up to six days. This indicated their uptake by intestinal stellate cells that acted as a depot for their release over time. Confocal microscopical examination of immunofluorescently-stained HSCs in liver sections, with considerable formula accumulation, confirmed HSCs-targeting and nuclear uptake. Consequently, V_A-coupled valsartan-loaded liposomes (VLC)-therapy resulted in profound re-expression of hepatic Mas-receptor and PPAR-γ, potent reduction of fibrogenic mediators' level and nearly normal liver function tests. Therefore, VLC epitomizes a promising antifibrotic therapy with exceptional extended action and additional PPAR-γ agonistic activity.	2018	https://www.sciencedirect.com/science/article/abs/pii/S0168365918302864
4	**Biologically-Guided Isolation of Natural Lead**	Pharmacology & Pharmacy	Hyperthyroidism is a common endocrine disorder associated with increased risk of cardiovascular complications and mortality. Although antithyroid drugs (ATDs) are approved as first line option for many hyperthyroidism cases, including pregnancy and childhood, they exert significant toxic profile.	2020	https://web.s.ebscohost.com/abstract?direct=true&profile=ehost&scope=site&authtype=crawler&jrnl=102

	Antithyroid Drug from Medicago sativa L. Sprouts and Its Toxic Profile in Comparison with Propylthiouracil.		Medicago sativa L. (alfalfa) also called "The father of all food" was among the diet consumed by mares that gave birth to foals with congenital hypothyroidism. Since, greenfeed was accused for the development of such condition, alfalfa may possess constituents with promising antithyroid potential that could be a valuable substitute for the conventional ATDs. The current work was designed to identify the most biologically active antithyroid phytoconstituent separated from alfalfa sprouts and comparing its antithyroid mechanism, efficacy and toxic profile to the standard ATD; propylthiouracil (PTU). The most biologically active solvent fractions from alfalfa sprouts extract were identified by in vitro screening for anti-thyroid peroxidase (TPO) activity, from which different phytoconstituents were separated and identified by interpretation of spectroscopic data. These compounds were then in vitro screened for anti-TPO and virtually screened via GLIDE XP docking into the crystal structures of the enzymes; bovine lactoperoxidase, as an alternative to TPO, and mammalian selenocysteine-dependent iodothyronine deiodinase (IDI), that are both uniquely dually prohibited by PTU. The compound that showed the least TPO IC₅₀ and highest combined docking XP score was elected for comparing its antithyroid mechanism, efficacy, tendency to reverse hyperthyroidism-triggered complications and toxicity to PTU using L-thyroxine-induced hyperthyroidism model in rats. Seven compounds (1-7) were isolated from the most biologically active fraction, whilst, compounds (4-7) were reported for the first time from alfalfa sprouts. Compound 5 (apigenin) showed the least TPO IC50 and highest in-silico combined score, thus, apigenin was selected for further in-vivo investigations. Apigenin was found to more effectively interfere with type 1-IDI than with TPO in vivo. Apigenin therapy resulted in nearly euthyroid state, without incidence of hypothyroidism, thyroid hypertrophy, hepatotoxity or WBCs count reduction. In addition, apigenin, but not PTU, corrected hyperthyroidism-induced left ventricular		19498&AN=146110181&h=Rx5jYVPz9ogJ0kildzyu%2fxcncab6CKVQ6%2fG8tzRN3FGaqzrX%2bYUKteBnrcwJwcba3aOcmmekpVs6D8aVz5BUTA%3d%3d&crl=c&resultNs=AdminWebAuth&resultLocal=ErrCrlNotAuth&crlhashurl=login.aspx%3fdirect%3dtrue%26profile%3dehost%26scope%3dsite%26authtype%3dcrawler%26jrnl%3d10219498%26AN%3d146110181

			hypertyrophy. Therefore, apigenin is a natural lead antithyroid drug that represents a possible safer alternative to conventional ATDs.		
5	**Vitamin B12 as a cholinergic system modulator and blood brain barrier integrity restorer in Alzheimer's disease**	Pharmacology & Pharmacy	So far, the cholinergic hypothesis of Alzheimer's disease (AD) remains the fundamental explanation for the complex etiopathology of AD. However, therapeutics raising synaptic acetylcholine (Ach) or having cholinergic receptors agonistic activity had shown limited clinical efficacy, possibly, due to lacking capability to aggregate cholinergic receptors within the degenerated cholinergic neurons. Vitamin-B12 (B12) is an epigenetic modifier. It has a specific CNS transport system via the cubam receptors. The later enclose a cholinergic aggregator; agrin protein, suggesting that B12 administration may cause cholinergic receptors aggregation. Further, B12 involvement in homocysteine (Hcy) metabolism may restore blood brain barrier (BBB) integrity disrupted by elevated Hcy levels in AD. Here in, using a pharmacological model of cholinergic amnesia, three different B12 doses were compared to the standard of care; donepezil (DON) regarding cholinergic system modulation, and their effect on Hcy metabolic pathways. Further, AD-associated cerebro-vascular pathology was assessed by morphometric analyses of cerebro-vasculature morphology and ultrastructure using scanning and transmission electron-microscopes, respectively. Consequent effect on key AD-hallmarks and behavioral cognitive tests was also examined. The highest B12-tested dose (B12-HD) showed the greatest hippocampal cholinergic modulation with dose-dependent preferential upregulation of one cholinergic receptor over the other. Altered Hcy metabolism was proved to be a consequence of cholinergic disruption that was variably reversed by different B12 doses. In spite of equipotent effect of DON and B12-HD therapies in decreasing β-amyloid synthesis, B12-HD-treated group revealed the greatest restoration of BBB integrity indicating superior capability of β-amyloid clearance. Therefore, B12-HD therapy may	2022	https://www.sciencedirect.com/science/article/pii/S0928098722000860

			represent a promising AD-modifying agent with extra-ability over conventional cholinergic modulators to aggregate cholinergic receptors.		
6	**Alleviation of Liver Cirrhosis and Associated Portal-Hypertension by *Astragalus* Species in Relation to their UPLC-MS/MS Metabolic Profiles: A Mechanistic Study.**	Pharmacology & Pharmacy	Liver cirrhosis is a late-stage liver disease characterized by excessive fibrous deposition triggering portal-hypertension (PH); the prime restrainer for cirrhosis-related complications. Remedies that can dually oppose hepatic fibrosis and lower PH, may prevent progression into decompensated-cirrhosis. Different *Astragalus*-species members have shown antifibrotic and diuretic actions with possible subsequent PH reduction. However, *A.spinosus and A.trigonus* were poorly tested for eliciting these actions. Herein, *A.spinosus* and *A.trigonus* roots and aerial parts extracts were subjected to comprehensive metabolic-fingerprinting using UHPLC-MS/MS resulting in 56 identified phytoconstituents, followed by chemometric untargeted analysis that revealed variable metabolic profiles exemplified by different species and organ types. Consequently, tested extracts were *in-vivo* evaluated for potential antifibrotic/anticirrhotic activity by assessing specific markers. The mechanistic prospective to induce diuresis was investigated by analyzing plasma aldosterone and renal-transporters gene-expression. Serum apelin and dimethylarginine-dimethylaminohydrolase-1 were measured to indicate the overall effect on PH. All extracts amended cirrhosis and PH to varying extents and induced diuresis via different mechanisms. Further, An OPLS model was built to generate a comprehensive metabolic-profiling of *A.spinosus* and *A.trigonus* secondary-metabolites providing a chemical-based evidence for their efficacious consistency. In conclusion, *A.spinosus* and *A.trigonus* organs comprised myriad pharmacologically-active constituents that act synergistically to ameliorate cirrhosis and associated PH.	2022	In press
7	**Novel Mucoadhesive Celecoxib-**	Pharmacology & Pharmacy	**Background:** Oral squamous-cell carcinoma (OSCC) is a widespread health problem. Myeloid-derived suppressor cells (MDSCs) are major tumor microenvironment (TME) population that governs many carcinogenesis	2022	In press

	loaded Cubosomal Sponges: Anticancer Potential and Regulation of Myeloid-Derived Suppressor Cells in Oral Squamous Cell Carcinoma		aspects by establishing immunosuppressive milieu favoring tumor aggressiveness and treatment resistance. Cyclooxygenase-2 (COX-2) regulates MDSCs activity, hence, COX-2-selective inhibition by celecoxib (CXB) showed good anticancer effect at relatively high doses with possible subsequent cardiovascular complications. Therefore, targeted CXB delivery to MDSCs may represent a promising OSCC treatment strategy. **Research design:** Novel mucoadhesive-cubosomal buccal sponges were prepared for MDSCs targeting and evaluated for their *in-vitro* quality attributes, *ex-vivo* mucoadhesion and deposition using buccal chicken-mucosa. **Results:** Optimally-selected formulation showed considerable uptake by $CD33^{+}/11b^{+}$MDSCs in human OSCC cell-line (SCC-4) when quantitatively analyzed by flow-cytometry and examined using confocal-laser microscope. Optimum formulations loaded with two low CXB doses (SP26, SP28) were promoted to *in-vivo* studies, using 4-nitroquinoline-1-oxide-induced OSCC in rats, and compared to their corresponding CXB gels. SP28 revealed the highest ability to decrease MDSC activation, recruitment and TME-immunosuppression in the isolated tumors. Consequently, SP28 exerted the greatest capacity to reduce histologic tumor grade, the OSCC-specific serum tumor markers levels, cancer hallmarks and stemness markers. **Conclusion:** CXB-loaded cubosomal sponges preferentially target MDSCs with noticeable anticancer potential and may exemplify novel mucoadhesive nano-carriers for OSCC treatment.		