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The Abstracts

Results: Choline deficiency was characterized by diastolic dysfunction with focal inflammation and cardiac interstitial fibrosis that resembles the features of diabetic cardiomyopathy. In the case of the concurrent presence of choline deficiency and diabetes mellitus, the functional impairment was preserved but the echocardiographic dimensions of the cardiac chambers were characterized by significant decreased left ventricle posterior wall thickness and dilation of the left atrium as compared to either the diabetic or choline-deprived rats alone ($p=0.041$ vs DM, $p=0.009$ vs CDD and $p=0.015$ vs C). VEGF-A cardiac immunohistochemical expression showed a significant increase in all groups compared to control, while the renal immunohistochemical expression was more intense in the DM group and was significantly suppressed in the DM +CD group. KIM-1 immunohistochemical expression showed a significant increase in the DM+CD group compared to all other groups ($p<0.001$versus the control and DM groups and $p<0.01$ versus the DM group).

Conclusion: Choline deprivation seems to aggravate the collagen deposition in the diabetic myocardium triggering however at the same time the transition of a restrictive type of cardiomyopathy to a potential dilated type. Furthermore, under choline deficiency conditions diabetic nephropathy is deteriorated which in turn increases the cardiovascular morbidity and mortality.

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Novel multipotent antihyperlipidemic - antioxidant derivatives as potential agents for neuroinflammation

Tzara A[1], Kleftaras A[1], Kourounakis A[1]
[1]*National And Kapodistrian University Of Athens, Athens, Greece*

Introduction: The multifactorial nature of many complex diseases, such as metabolic syndrome, cancer and neurodegeneration, is shifting scientific research interest towards a multitarget approach; compounds, bearing a combination of two pharmacophores, each directed towards a different pharmacological target, seem to be a more suitable strategy to tackle such pathological conditions.
Squalene synthase (SQS) inhibitors, apart from acting as antihyperlipidemic agents, have been further directed towards various other potential therapeutic areas such as Alzheimer's or cancer. Imbalance in cell cholesterol levels may lead to alterations in neuronal cell membranes, influencing neuronal survival and therefore the course of Alzheimer's2. At the same time, there has been a scientific return towards cholinergic modulation in Alzheimer's, as part of a multitherapy approach3.

Objectives: This project involves the investigation of a series of multipotent molecules 1-5, combining moieties with antioxidant, anti-inflammatory and squalene synthase (SQS) inhibitory properties as an extension of a previous study.1

Methods: The newly designed compounds were synthesized in good yields, characterized via 1H and 13C NMR spectroscopy and pharmacologically evaluated, both in vitro and in vivo, for their antioxidant, anti-inflammatory, anti-hyperlipidemic and potential anti-neurodegenerative activity. Antioxidant activity was evaluated in vitro via inhibition of microsomal-membrane lipid-peroxidation and free-radical scavenging, as well as in vivo by determining total antioxidant capacity. Anti-inflammatory properties were studied in vitro, via inhibition of the enzyme lipoxygenase, and in vivo in an paw-edema protocol. Antihyperlipidemic activity was evaluated in vivo while inhibition of the enzyme acetylcholinesterase was determined in vitro.
Results: All new derivatives successfully maintained or even exceeded the antioxidant activity of their parent molecules, in the corresponding assays, with the most active compound 4 bearing an IC50 of 0.6 μM for lipid peroxidation. They also demonstrated satisfactory activity as lipoxygenase inhibitors, bearing IC50 values between 140-190 μM, significantly increased compared to all parent molecules. The new compounds also reduced in vivo carrageenan-induced mouse paw edema by 35-45%. All compounds reduced lipidemic parameters in vivo, with compound 1 being the most active antihyperlipidemic agent, reducing lipidemic parameters (total cholesterol and triglycerides) by approx. 50%. Finally, the in vitro acetylcholinesterase inhibition, as a potential "anti-neurodegenerative" indication, showed that several of the newly designed molecules inhibited the enzyme's activity by 31-42% at a concentration of 300μM.

Conclusion: The improved antihyperlipidemic, antioxidant and anti-inflammatory activity of the new under investigation derivatives, provide an interesting basis for their potential application not only in cardiovascular disorders but further in interlinked neuroinflammatory conditions. Further investigation of these multipotent derivatives may render them a promising therapeutic approach towards such interrelated conditions.

1 Matralis, AN; Kourounakis, AP. ACS Med. Chem. Lett. 2019, 10(1), 98-104
2 Kourounakis AP; Bavavea E. Arch. Pharm. (Weinheim) 2020, 353(9):e2000085
3 Douchamps, V; Mathis, C. Behav. Pharmacol. 2017, 28, 112-123

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Perspective for the development of new medicines based on purified Naftalan oil for the treatment of dermatological diseases

Zaychenko G[1], **Horbach A[1]**
[1]*Department of Pharmacology, Bogomolets National Medical University, Kyiv, Ukraine*

Introduction: Psoriasis is a complex, chronic inflammatory disease of the skin, manifested in little red and scaly plaques on any part of the body. Topical drugs are used to treat dermatological conditions, particularly psoriasis, effectively. Dermal drugs should include the following pharmacological activities: affect psoriatic inflammation, keratinocyte hyperproliferation, and angioproliferation.

Objectives: The study's primary is the scientific substantiation of the search for new drugs that have a complex effect on the main pathogenesis links of psoriasis and have a favourable safety profile. For 60 years, ointments with petroleum products have been used for treating psoriasis. The previous generation, which contained crude Naftalan oil, had several disadvantages (specific oil odour, dark brown colour, contaminated clothing, and bedding). Prolonged use of crude Naftalan oil led to dry skin, toxic liver damage, and was carcinogenic

Methods: Pharmacological analysis of medicinal properties of promising topical drugs based on purified Naftalan oil for the treatment of dermatological diseases.

Results: The new generation of new topical dosage forms proposed contain purified Naftalan oil, more saturated with gapans and steranes, standardized according to the European Pharmacopoeia, free of harmful organoleptic properties, and with improved pharmacological properties, and safer, reduced overall and dermal toxicity. Urea and drotaverine have been added to enhance the pharmacological action of new drugs with purified Naftalan oil. According to the projected data, such drugs should have pharmacological action: wound healing, keratolytic, antimicrobial, analgesic, and photoprotective.

Conclusion: The development of new drugs in mild dosage forms based on purified Naftalan oil will effectively treat chronic dermatological diseases, such as psoriasis. There are many medicines for the topical treatment of dermatological conditions. The use of new drugs may, in the long run, reduce doses of corticosteroids and expand the range of medications used to treat dermatological diseases such as psoriasis.

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The RASGRP1.rs8032939 in Kazakhstani patients with Seropositive Rheumatoid arthritis

Nurgaziyev M[1], Issilbayeva A[1,2], Ainabekova B[2], Zhetkenev S[1], Meiramova A[1,2], Ahmetova Z[1,2], Kushugulova A[1]
[1]*Laboratory of Human Microbiome and longevity, Center for life sciences, National Laboratory Astana, Nazarbayev University, Nur-Sultan, Kazakhstan*
[2]*NJSC Medical University Astana, Department of internal Medicine with the course of gastroenterology, endocrinology and pulmonology, Nur-Sultan, Kazakhstan*

Introduction: Rheumatoid arthritis (RA) is an autoimmune disease characterized by a genetic predisposition. Seropositive (RF+) form of this disease is the most common one. We studied the relationship between single nucleotide polymorphisms (SNP) RASGRP1.rs8032939 with RA in Kazakhstanis.
Objectives: Our study aims to investigate whether there are genetic links with RF status in Kazakhstani patients with RA.

Methods: We enrolled 70 RA patients all female and 113 healthy control subjects. The blood was collected to the test tubes with EDTA. The Genomic DNA was extracted using Promega Wizard genomic DNA Purification Kit according to manufacturer`s protocol. All DNA samples were stored at -20°C temperature. We genotyped all samples for RASGRP1.rs8032939 by Real-time polymerase chain reaction (RT-PCR) using TaqMan technology. Comparison of genotypes distribution between RA patients and healthy controls was carried out by the Chi-square ($\chi 2$) test, an odds ratio (ORs) and 95% confidence intervals (95% CIs) were used. Correlation of the associated SNP with Rheumatoid factor (RF) status among RA cases was performed with $\chi 2$ test.

Results: We hadn`t revealed any significant predominance of RASGRP1.rs8032939 in RA patients group compared to healthy subjects. Stratifying the data by RF presence, a significant association was revealed between the C/T genotype of RASGRP1 and seropositive (RF+) RA patients (OR= 4.67 [95CI 1.42-15.31], p= 0.00776) in overdominant mode of inheritance and in codominant mode of inheritance (OR= 2.33 [95CI 0.54-10.14], p= 0.00512).

Conclusion: Our study had revealed strong association between RASGRP1.rs8032939 and RF+ RA form. We need further studies on larger cohorts to confirm and be able to extrapolate our results.

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Effects of type 2 diabetes treatment on TNFα plasmatic concentrations in the neuropathy risk

Balderas Vazquez C[1], Valenzuela Limón O[2], Bernal Morales B[1], García Montalvo E[2], Rodríguez Landa J[1], Balderas Vazquez C[1]
[1]*Instituto de Neuroetología, Universidad Veracruzana, Xalapa, México*
[2]*Facultad de Ciencias Químicas, Universidad Veracruzana, Orizaba, México*

Introduction: The type 2 diabetes is a complex disorder frequently found amongst populations that involves the pancreas and insulin system. Manage patients include dietary adequacy and pharmacology treatment metformin. The tumor necrosis factor alpha (TNFα) is a pleiotropic pro-inflammatory cytokine involved in the mechanism of neuroinflammation. Several studies have researched the relationship between drugs approved for management of type 2 diabetes and its anti-inflammatory properties, but in Mexico especially Veracruz these studies are scarce. Aim: Assess the effect of pharmacology treatment on TNFα plasmatic concentrations and its association with protective role on peripheral neuropathy in diabetic patients of the central zone in Veracruz. Materials and methods: A cross sectional study was conducted according to a prior approval by an ethical committee. The study included participants with diagnostic of type 2 diabetes. Each participant signed the informed consent letter. Demographic and clinical aspects were explored by questionnaires. Neuropathy symptoms were assessed by Neuropathic Pain Questionnaire. Blood samples were obtained by venipuncture to assess