PL-1
Sustainable utilization of medicinal plants and potential drug candidates from some Turkish plants

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Medicinal plants have virtually untapped reserve of original drug molecules which await determination, chemical and biological investigation. Such development may also deliver a valuable asset for local people who can benefit from the exploitation of their natural sources. Besides, some of these plants are endangered species and documentation of their potential usefulness may help to ensure their conservation and even lead to programs for sustainable development. Therefore, biodiversity must be treated more seriously as a global source, to be indexed, used and preserved.
There is still a great need for novel compounds with unique mechanisms of action to treat diseases such as cancer, Alzheimer's, diabetes and arthritis. Furthermore, multiresistance development by the parasites to the current drugs also constitutes another problem for the treatment of parasitic diseases as well as tuberculosis. New chemotherapeutic tools are also needed.
The key to success of discovering therapeutic agents from bioresources is based on bioassay-directed isolation techniques. Sensitive bioassays and mechanism-based screening protocols as well as information of folkloric utilization of plants have led to the discovery of new drug candidates. Sustainable utilization of medicinal plants and the recent results from Turkish medicinal plants will be discussed.

PL-2
Artemisia annua volatiles: aN interesting by product with cosmetic and medicinal applications

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Artemisia annua L. (Asteraceae) is an aromatic annual herb endemic to the northern parts of Chahar and Suiyuan provinces in China. However, the plant now grows wild in Europe and America and it is cropped on a large scale in China, Vietnam, Turkey, Iran, Afghanistan and Australia. *A. annua* is an important medicinal plant and it is mostly known as the source of a unique antimalarial constituent, artemisinin. The foliage and inflorescence of *A. annua* plants also yield an essential oil upon hydrodistillation, which could represent another potential commercially valuable product. The oil is characterized by a large number of terpenoids, whose composition and yields are related to the cultivars and developmental stage of the plant. Characteristic constituents are artemisia ketone and artemisia alcohol but their content is extremely variable and can also be absent, other constituents are camphor, 1,8-cineole, and germacrene D. Volatiles are also present in the aromatic waters which can represent another source of commercially valuable product for cosmetic use. Some biological activities have been attributed to the essential oil or its components: antibacterial (Enterococcus sp), antifungal (Saccaromices cerevisiae and Candida albicans), and antioxidant. 1,8-Cineole was active against Tribolium castaneum for contact toxicity, fumigant toxicity, and antifeedant activity.

PL-3
Englerins, novel plant products with specific activity in renal cancer models

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We recently reported the isolation of the novel guaiane sesquiterpene esters englerins A and B from the Tanzanian plant *Phyllanthus engleri* (Euphorbiaceae), based on the activity of the crude extract in the NCI 60-cell screen. The extract was selected by a global bioinformatics analysis of all extract testing data to identify those extracts which preferentially inhibited the growth of kidney cancer cell lines. Englerin A demonstrated excellent selectivity against 5 of 8 renal cancer cell lines, with low nanomolar potency. We serendipitously discovered a series of chlorinated englerins, some of which have similar biological activity and contribute to an understanding of structure-activity relationships in the series. We have also explored the biological basis of this selectivity and have conducted several xenograft studies in mice with englerin A. Large scale isolation of englerin A from the plant is underway at the NCI to support further studies.

PL-4
Secretory structures in Balkan's species of hypericum l.: A model system for species discrimination

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Hypericum species are characterized by presence of secretory structures, situated on leaves and flower parts, mainly sepals and petals. Secretory tissues (black nodules, translucent glands, secretory channels) are sites of synthesis and accumulation of active substances. Secretory structures are an important feature for species identification and subgeneric classification. Distribution of secretory structures within plant organs, their number and size were analyzed in 15 species from the Balkan region, including both widely distributed species and locally rare and/or endemic ones (e.g. *H. richeri*, *H. rumeliacum*, *H. cerastoides*). The highest number of leaf marginal and laminar black nodules was determined for *H. richeri* (3.85 ± 0.53 per mm^2) and *H. perforatum* (0.93 ± 0.26), respectively. The largest translucent glands were found on leaves of *H. maculatum* (126.29 ± 19.2 μm), but absent in few studied species, such as *H. alpigenum* and *H.*

richeri. Differences in secretory structures were studied by analysis of variance (ANOVA) and application of multivariate statistics (discriminant analysis, correspondence analysis, cluster analysis) to estimate whether such variability is related to classification systems of the genus. Preliminary study on possible relations between hypericine content and secretory structures in several chosen species showed significance of size of leaf black nodules.

PL-5

Recent advances in phytochemistry of bryophytes: chemical diversity and biological activity

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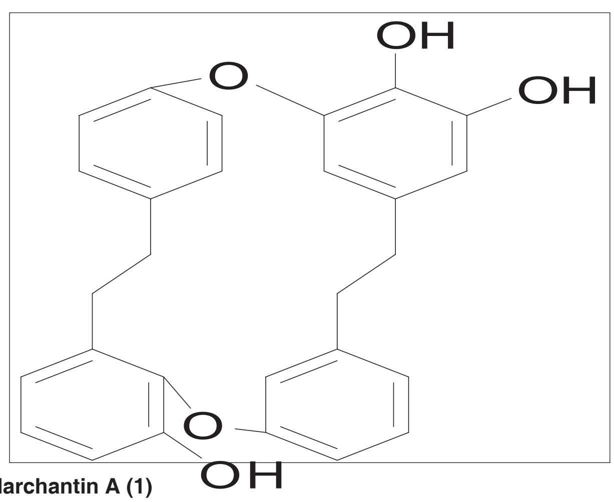
The present paper concerns with secondary metabolites and their biological activity of the Marchantiophyta (=liverworts) [Fig.1]. Almost all liverworts possess beautiful cellular oil bodies [Fig. 2]. Over several hundred new compounds have been isolated from bryophytes. More than 40 new carbon skeletal terpenoids have been found in liverworts. Liverworts are also rich sources of bis-bibenzyl [e.g. Marchantin A (1)] which are one of the most characteristic compounds from the liverworts. It is also noteworthy that most of sesqui- and diterpenoids found in the liverworts are enantiomers of those found in higher plants. Some

Figure 1: Ptychanthus striatus



Marchantin A (1)

Figure 2: Oil bodies of Frullania species

of the isolated compounds from liverworts show characteristic scents, pungency and bitterness, allergenic contact dermatitis, cytotoxicity, anti-HIV and DNA polymeraseβ inhibition, antimicrobial and antifungal activity, insect antifeedant and mortality, nematocidal activity, superoxide anion radical release, 5-lipoxygenase, calmodulin, hyaluronidase, cyclooxygenase and NO production inhibitory activity, and plant growth inhibition, neurotrophic and muscle relaxing activity, cardiotonic, piscicidal and anti-obesity activity [1-4].

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PL-6

Phytochemicals with diverse pharmacological activity from medicinal plants; are they panacea to cure all?

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Plants have become a resource for protection of health and treatment of ailments for human being since the beginning of history. Whole plants or their extracts which were used as remedy for thousands of years by man had yielded active pharmaceutical agents as a consequence of the progresses in chemistry and pharmacological methods after 19th century. However, due to loss of the synergistic or antagonistic interactions inside the active extracts during this purification processes, most of these pure phytochemicals exerted lesser efficieny then their original extracts. Therefore it has recently rediscovered that synergistic or antagonistic interactions in herbal extracts are crucial for efficiency and safety.

Another recently introduced strategy in the western phytotherapy system is "Multitarget Therapy". Designation and combination of different plants parts with diverse activity characteristics to produce a medicinal cocktail would activate different mechanisms for fighting the diseases symptoms via synergistic interactions less harmful to the healthy tissues of the body. Actually, this concept has been practised in Traditional Chinese Medicine since thousands of years.

Apart from these two main concepts, an ever-expanding body of pharmacological and clinical evidences have accumulated regarding the phytochemicals with "Multivalent activity" profiles. As opposed to chemically synthetised drugs, which provide a single target for a single receptor as the mechanism of action, such phytochemicals are able to up- or down-regulate signaling pathways, gene transcription, cellular metabolism, etc., and thus assist in the regulation of the general physiological status of the cell and/or organism in response to stressors posed by both intracellular and extracellular conditions. This presentation highlighs multivalent effects of several phytochemicals i.e., flavonoids (isoorientin, isoquercitrin), iridoids (aucubin, catalpol) experimentally proven.

PL-7

Content and qualitative properties of essential oil of *Chamaemelum nobile* (l.) All. Of slovak proveniencie

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The work deals with qualitative and quantitative composition of the essential oil from selected cultivars of *Chamaemelum nobile* (L.) All. Essential oil was obtained by hydrodistillation. The constituents were identified by the GC/MS method. We have identified 49 constituents and followed the representation of major and minor essential oil components in selected cultivars during three vegetation periods. The dominant constituents were: isobutylangelate, isoamylangelete, isobutylbutyrate, isobutylmethacrylate, myrcene, α-pinene, caryophylene, limonene, α-bisabolol, farnesol and others. The quality of essential oil did not depend on season so much as its chemical composition.

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PL-8

New generation techniques for essential oil extraction

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Essential oils are the volatile parts of the secondary metabolites of plants. Plants having essential oil have been used for their medicinal, flovour and fragrance properties. Most commercially used essential oils are monoterpenes. However, the essential oils are highly complex and can include oxygenated compounds (alcohols, aldehydes, ketones, acids, phenols, oxides, lactones, acetals, ethers and esters) apart from pure hydrocarbons. Essential oil of has usually been isolated by either traditional hydro-distillation or steam-distillation. Losses of some volatile compounds, long extraction times, degradation of unsaturated or ester compounds through thermal or hydrolytic effects are the principal disadvantages of these extraction methods. Therefore, various techniques for obtaining essential oils have been developed recently. These techniques are as follows: microwave-assisted distillations (MAD) (with solvents, without solvent, rotatory, in situ, solvent-free microwave improved by using carbonyl iron powder, microwave hydrodiffusion and gravity), Solvent extraction (SE), supercritical fluid extraction (SFE), ultrasonically assisted extraction in combination with under vacuum distillation, and extraction done by using Naviglio extractor. It was evident that it was posible to get qualified and sufficent yield of essential oil from plants by applying various sophisticated methods alternative to conventional hydrodistillation methods.

PL-9

Recent investigations on the chemistry and cytotoxic activity of steroid and triterpene glycosides from african and asian bioresources

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Saponins are steroid or triterpene glycosides offering a great molecular and biological diversity. Their activities are often related to their membrane interacting properties, resulting in potential toxic or specific biological effects which have been reviewed (cytotoxic, antitumor, immunoadjuvant, antiviral, analgesic, anti-inflammatory, antifungal, antibacterial, hypocholesterolemic, hypoglycemic ....to mention just a few).

Our laboratory has focussed in recent years on the isolation, structure elucidation of cytotoxic and immunostimulant/ immunoadjuvant saponins, mainly from the African and Asian plant biodiversity.

This lecture will highlight some relevant examples of new steroid saponins from species of ***Dioscorea*** (Dioscoreaceae), ***Chlorophytum, Asparagus*** (Liliaceae) and triterpene saponins from species of ***Polygala, Muraltia***, ***Carpolobia***, ***Atroxima***, ***Nylandtia***, ***Securidaca,*** (Polygalaceae), ***Eryngium*** (Apiaceae), ***Cyclamen*** (Primulaceae), ***Astragalus*** (Fabaceae), ***Albizia*** (Mimosaceae), ***Zygophyllum*** (Zygophyllaceae), ***Cussonia*** (Araliaceae), ***Silene***, ***Arenaria***, ***Acanthophyllum,*** and ***Paronychia*** (Caryophyllaceae). Our strategy combines isolation procedures by successive chromatographic steps [flash chromatography, vacuum liquid chromatography (VLC), medium-pressure liquid chromatography (MPLC), and HPLC] and structural elucidation by extensive spectroscopic methods including 1D, 2D NMR, FABMS and HRESIMS. The biological assays included mainly cytotoxicity on human HT-29 and HCT 116 colon cancer cells, immunoproliferation and apoptosis induction of Jurkat cells and splenocytes. The discussion will also focus on the understanding of their mechanism of action and structure/activity relationships.

PL-10

The effects of herbal extracts on insulin releasing cells

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Pancreatic β-cells are responsible for insulin secretion that regulates blood glucose homeostasis. β-cell dysfunction, contributes to the pathophysiology of type 1 and type 2 diabetes.[1] Insulin secretion is subject to control by nutrients and by hormonal, neural, and pharmacological factors. Among these, glucose is by far the most important regulator of the machinery of insulin secretion.[1] It has been demonstrated that glycolytic and oxidative events coupled with the generation of reactive oxygen species (ROS) lead to accelerated ATP generation and are key transduction phenomena in β-cell signaling.[2] Chronic hyperglycemia as in the case of diabetes has been shown to be involved in β-cell dysfunction, a phenomenon known as glucotoxicity.[2,3] Although multiple biochemical pathways and mechanisms of action for glucose toxicity have been suggested, the cellular redox imbalance due to increased oxidative stress (OS) seems to be a common key factor.[2,3] Apoptosis is probably the main way of β-cell death in the presence of unmitigated hyperglycemia and OS. Cytokines contribute to accelerated β cell apoptosis and death in the presence of glucotoxicity and OS.[4] In addition, H_2O_2 may induce β-cell injury via oxidative stress (OS).[5] Therefore, the protection of β-cell function is important to prevent diabetes, and whatever treatment approach is chosen, the therapeutic response is strongly dependent on the actual β-cell function. As in the case of studies on the retardation of diabetes-induced complications by antioxidants, the greater attention is now focused on natural herbal antioxidants in the protection of β-cells against OS-mediated injury.[6,7] In this context, we investigated the effects of polyphenolic olive extracts and oleuropein against H_2O_2- and cytokines-induced cytotoxicity in pancreatic β-cell line, INS-1E.[8-10] Cells were separately preincubated (24 h.) with 0.1mmol/L oleuropein, 0.1mg/mL olive leaf extract and 0.1mg/mL olive fruit extracts. Cytotoxicity was induced by incubation (6 h.) of H_2O_2 (0.035 mmol/L) or different cytokine cocktails (IL-1β + TNF-α + IFN-γ). Cell viability was measured with colorimetric MTT reduction assay. Intracellular reactive oxygen species (ROS) was observed with DCF-DA assay. Living, necrotic and apoptotic cell numbers was detected with Acridine orange/ethidium bromide staining under flourescent microscopy. We also measured insulin release with ELISA kit; caspase activity with flourometric assay kit, cytochrome c releasing with western blot method and antioxidant glutathione (GSH) levels and enzymes such as superoxide dismutase (SOD) and catalase (CAT) and glutathione peroxidase (GPx) with spectrophotometric technique. Olive extracts and standard oleuropein showed significant decrease in H_2O_2-stimulated intracellular ROS generation. The leaf extract significantly increased the number of living cells, reduced necrotic cell number, protected GPx, inhibited SOD and over activated CAT, but had no significant effect on insulin secretion in H_2O_2-treated INS-1E cells. Standard oleuropein recovered insulin release with partly increasing the number of living cell, activated CAT, but had no effect on GPx. Both the olive leaf extract and standard oleuropein had no effect on the number of apoptotic cells in H_2O_2-treated INS-1E cells. Generally, incubation with cytokines were decreased cell viability, living cell number, insulin release, intracellular glutathione levels and SOD activity, and also increased ROS production, apoptotic and necrotic cell number and caspase activity. Olive leaf extract was demonstrated protective effects via increasing living cell number and SOD activity, decreased apoptotic cell number and caspase activity, and activated insulin release in cytokine treated cells. Glutathione levels were significantly increased with preincubation all olive samples. Cytochrome c releasing unchanged either by cytokine cocktail, oleuropein or by olive extracts. These results justify the ethno medical use of olive in the management of diabetes and may contribute to understanding the mechanisms.

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