

Natural products-inspired discovery and development of novel antimicrobial, anti-inflammatory and antiplatelet agents

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We have extensively worked on several medicinally important plants used in the traditional Indian and Chinese systems of medicine and isolated a large number of novel compounds belonging to different classes (alkaloids, polyphenols, steroids, amides, terpenoids, etc.). Several of these compounds have shown interesting biological activities, remarkable of them has been our extensive work on polyphenol acetates leading to the discovery of a fundamental biochemical pathway involving acetyl CoA-independent enzymatic protein acetylation. Our seminal investigations have highlighted the unique biochemical and pharmacological action of polyphenol acetates. These act as the substrates for the well-known protein calreticulin and transfer acetyl groups to certain receptor enzymes, such as cytochrome P-450 linked mixed function oxidases (MFO), NADPH cytochrome c reductase, Nitric Oxide Synthase (NOS), protein kinase c (PKC) and glutathione S-transferase (GST) resulting in modulation of their catalytic activities. The purified enzyme from buffalo liver in the presence of 7,8-diacetoxy-4 methylcoumarin (DAMC) and several other polyphenol acetates was found to significantly enhance the NOS activity in human platelets and caused significant vasorelaxation. These polyphenol acetates and several natural products were also found to lower PKC levels and suppress the ICAM-1 and VCAM-1 expression and were found to be good anti-inflammatory & anti-asthmatic agents. Further, acetyl polyphenols and several other classes of natural products were also found to be excellent inhibitors of chemical and radiation induced clastogenicity, and antimicrobial agents against various deadly fungal & bacterial infections viz. botulism and aspergillosis.

Details of these studies will be presented at the Symposia.

Key References:

E Kohli, M Gaspari, HG Raj, VS Parmar, SK Sharma, J van der Greef, R Kumari, G Gupta, Seema, P Khurana, YK Tyagi, AC Watterson and CE Olsen. Acetoxy drug: protein transacetylase of buffalo liver — characterization and mass spectrometry of the acetylated protein product. *Biochimica et Biophysica Acta* **1698**, 2004, 55– 66.

S Kumar, P Arya, C Mukherjee, BK Singh, N Singh, VS Parmar, AK Prasad and B Ghosh. Novel aromatic ester from *Piper longum* and its analogues inhibit expression of cell adhesion molecules on endothelial cells. *Biochemistry* **44**, 2005, 15944-15952.

ME Bracke, BWA Vanhoecke, L Derycke, S Bolca, S Possemiers, A Heyerick, CV Stevens, DD Keukeleriem, HT Depypere, W Verstraete, CA Williams, ST McKenna, S Tomar, D Sharma, AK Prasad, AL DePass and VS Parmar. Plant polyphenolics as anti-invasive cancer Agents. *Anticancer Agents in Medicinal Chemistry* **8**, 2008, 171-185.

A Goel, AK Prasad, VS Parmar, B Ghosh and N Saini. Apoptogenic effect of 7,8-diacetoxy-4-methylcoumarin and 7,8-diacetoxy-4-methylthiocoumarin in human lung adenocarcinoma cell line: Role of NF- κ B, Akt, ROS and MAP kinase pathway. *Chemico-Biological Interactions* **179**, 2009, 363-374.

AK Chillar, V Yadav, A Kumar, M Kumar, VS Parmar, AK Prasad and GL Sharma. Differential expression of *Aspergillus fumigatus* protein in response to treatment with a novel antifungal compound, diethyl 4-(4-methoxyphenyl)-2,6-dimethyl-1,4-dihydropyridin-3,5-dicarboxylate. *Mycoses* **52**, 2009, 223-227.

V Kumar, S Kumar, M Hassan, H Wu, RK Thimmulappa, A Kumar, SK Sharma, VS Parmar, S Biswal and SV Malhotra. Novel chalcone derivatives as potent Nf2 activators on mice and human lung epithelial cells. *Journal of Medicinal Chemistry* **54**, 2011, 4147-4159.

K Macáková, Z Reháková, P Mladenka, J Karlícková, T Filipický, M Ríha, AK Prasad, VS Parmar, L ek Jahodár, P Pávek, R Hrdina and L Saso. In vitro platelet antiaggregatory properties of 4-methylcoumarins. *Biochimie* 2012, **94**, 2681-2686.

A Kumar, S Sushama, S Manral, S Sinha, R Joshi, U Singh, V Rohil, AK Prasad, VS Parmar and HG Raj. Calreticulin transacetylase mediated activators of human platelet nitric oxide synthase by acetyl group donor compounds. *Nitric Oxide: Biology and Chemistry* **26**, 2012, 9-19.

S Kumar, BK Singh, AK Prasad, VS Parmar, S Biswal and B Ghosh. Ethyl 3',4',5'-trimethoxythionocinnamate modulates NF- κ B and Nrf2 transcription factors. *European Journal of Pharmacology* **700**, 2013, 32–41.

S Kumar, S Malhotra, AK Prasad, EV Van der Eycken, ME Bracke, WG Stetler-Stevenson, VS Parmar and B Ghosh. Anti-inflammatory and antioxidant properties of *Piper* species: A perspective from screening to molecular mechanisms. *Current Topics in Medicinal Chemistry* **15**, 2015, 886-893.

K Venkateswaran, A Shrivastava, PK Agrawala, AK Prasad, N Kalra, PR Pandey, K Manda, HG Raj, VS Parmar and BS Dwarakanath. Mitigation of radiation-induced hematopoietic injury by the polyphenolic acetate 7, 8-diacetoxy-4-methylthiocoumarin in mice. *Nature Scientific Reports* **6:37305**, 2016, DOI: 10.1038/srep37305 (pp. 1-20).

M Balhara, R Chaudhary, S Ruhil, B Singh, N Dahiya, VS Parmar, PK Jaiwal and AK Chhillar. Siderophores; iron scavengers: The novel and promising targets for pathogen specific antifungal therapy. *Expert Opinion on Therapeutic Targets* **20**, 2016, 1477-1489.

S Malhotra, S Singh, N Rana, S Tomar, P Bhatnagar, M Gupta, SK Singh, BK Singh, AK Chhillar, AK Prasad, C Len, P Kumar, KC Gupta, AJ Varma, RC Kuhad, GL Sharma, VS Parmar and NGJ Richards. Chemoenzymatic synthesis, nanotization and anti-*Aspergillus* activity of optically enriched fluconazole analogues. *Antimicrobial Agents and Chemotherapy* **61**, 2017, e00273-17, doi:10.1128/AAC.00273-17.

VD Kancheva, AK Slavova-Kazakova, SE Angelova, SK Singh, S Malhotra, BK Singh, L Saso, AK Prasad and VS Parmar. Protective effects of 4-methylcoumarins and related compounds as radical scavengers and chain-breaking antioxidants. *Biochimie* **140**, 2017, 133-145.

HK Tiwari, P Kumar, N Jatana, K Kumar, S Garg, L Narayanan, PS Sijwali, KC Pandey, N Yu Gorobets, BN Dunn, VS Parmar and BK Singh. In vitro antimalarial evaluation of piperazine- and piperazine-based chalcones: Inhibition of falcipain-2 and plasmeprin II hemoglobinas activities from *Plasmodium falciparum*. *Chemistry Select* **2(25)**, 2017, 7684-7690.

K Venkateswaran, A Verma, AN Bhatt, A Shrivastava, K Manda, HG Raj, AK Prasad, C Len, VS Parmar and BS Dwarakanath. Emerging roles of calreticulin in cancer: Implications for therapy. *Current Protein & Peptide Science* **19**, 2018, 344-357.

VD Kancheva, AK Slavova-Kazakova, SE Angelova, P Kumar, S Malhotra, BK Singh, L Saso, AK Prasad and VS Parmar. Protective effects of new antioxidant compositions of 4-methylcoumarins and related compounds with DL- α -tocopherol and L-ascorbic acid. *Journal of the Science of Food and Agriculture* **98**, 2018, 3784-3794.

E Profumo, B Buttari, L Tinaburri, D. D'Arcangelo, M Sorice, A Capozzi, T Garofalo, A Facchiano, R Businaro, P Kumar, BK Singh, VS Parmar, L Saso and R Rigano. Oxidative stress induces HSP90 up-regulation on the surface of primary human endothelial cells: Role of the antioxidant 7,8-dihydroxy-4-methylcoumarin to prevent HSP90 exposure to the immune system. *Oxidative Stress and Cellular Longevity* **2018**, 2018, Article ID 2373167, 9 pages, doi: 10.1155/2018/2373167.

KB Patel, S Cai, M Adler, BK Singh, VS Parmar and BR Singh. Natural compounds and their analogues as potent antidotes against the most poisonous bacterial toxin. *Applied and Environmental Microbiology* **84**, 2018, DOI:10.1128/AEM.01280-18.

K Venkateswaran, A Shrivastava, PK Agrawala, AK Prasad, SC Devi, K Manda, VS Parmar and BS Dwarakanath. Mitigation of radiation-induced gastro-intestinal injury by the polyphenolic acetate 7, 8-diacetoxy-4-methylthiocoumarin in mice. *Nature Scientific Reports* **9:14134**, 2019, <https://doi.org/10.1038/s41598-019-50785-x> (pp. 1-17).

S Dahiya, AK Chhillar, N Sharma, P Choudhary, A Punia, M Balhara, K Kaushik and VS Parmar. *Candida auris* and nosocomial infection. *Current Drug Targets* **21**, 2020, 365-373.

K Venkateswaran, A Shrivastava, AK Prasad, VS Parmar and BS Dwarakanath. Developing polyphenolic acetates as radiation countermeasure agents: Current status and future perspectives. *Drug Discovery Today* **25**, 2020, 781-786.

KB Patel, O Kononova, S Cai, V Barsegov, VS Parmar, R Kumar and BR Singh. Botulinum neurotoxin inhibitor binding dynamics and kinetics relevant for drug design. *Biochimica et Biophysica Acta (BBA) – General Subjects*, 2021, <https://doi.org/10.1016/j.bbagen.2021.129933>.

A Kumar, P Kaushik, S Incerpi, JZ Pedersen, S Goel, AK Prasad, V Rohil, VS Parmar, L Saso and C Len. Evaluation of the free radical scavenging activities of ellagic acid and ellagic acid peracetate by EPR spectrometry. *Molecules* **26**, 2021, 4800. <https://doi.org/10.3390/molecules26164800>.

S Dahiya, N Sharma, A Punia, P Choudhary, P Gulia, VS Parmar and AK Chhillar. Antimycotic drugs and their mechanisms of resistance to *Candida* species. *Current Drug Targets* **23**, 2022, 116-125.

K Venkateswaran, A Shrivastava, PK Agrawala, AK Prasad, K Manda, VS Parmar and BS Dwarakanath. Immune-modulation by 7, 8-diacetoxy-4-methylthiocoumarin in total body-irradiated mice: Implications for the mitigation of radiation-induced hematopoietic injury. *Life Sciences* **311**, 2022, <https://doi.org/10.1016/j.lfs.2022.121140>.

A Behl, S Solanki, SK Paswan, TK Datta, AK Saini, RV Saini, VS Parmar, VK Thakur, S Malhotra and AK Chhillar. Biodegradable PEG-PCL nanoparticles for co-delivery of MUC1 inhibitor and doxorubicin for the confinement of triple-negative breast cancer. *Journal of Polymers and the Environment* **31**, 2023, 999-1018.

A Behl, ZA Wani, NN Das, VS Parmar, C Len, S Malhotra and AK Chhillar. Monoclonal antibodies in breast cancer: A critical appraisal. *Critical Reviews in Oncology/Hematology* **183**, 2023, 103915.

HK Sharma, P Gupta, D Nagpal, M Mukherjee VS Parmar and V Lather. Natural compounds as the prospective inhibitors of antibacterial drug resistance targets in *Staphylococcus aureus*. *Fitotrepia* **170**, 2023.