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Review Article

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Veliparib for the treatment of solid malignancies

Rony R George, Rimisha Thomas, Anna Davice and Meby S Mathew

Abstract

Objective: Veliparib is a poly adenosine diphosphate ribose polymerase (PARP) −1 and −2 inhibitor with chemo-sensitizing and anticancer activities that has shown promising results in early-phase trials. The aim of this comprehensive review is to summarise the profile of veliparib and to provide an overview of its early clinical investigations.

Data Sources: Details of all the completed trials evaluating the profile of veliparib were identified from ClinicalTrials.gov with the relevant keywords. Furthermore, databases such as Google Scholar and PubMed were searched using the National Clinical Trial (NCT) number to retrieve publications of results not listed in the trial registry.

Data Summary: A total of 25 completed clinical trials indicating the use of veliparib in solid malignancies were identified. The results showed that veliparib is well tolerated, both as a single agent and in combination with standard chemotherapy doses. Being a broad-spectrum potentiator of DNA-damaging agents and radiation, it has shown to improve the clinical outcomes, particularly in solid tumors like ovarian cancer, breast cancer and lung cancer.

Conclusions: The results from clinical trials indicate that veliparib can be an excellent therapeutic strategy for BRCA mutation associated cancers and tumors bearing deficiencies in the HR pathway as well. Further studies establishing the dosing, sequence of therapy, extended use and compatibility with various anti-cancer drugs are warranted to define its exact role in cancer therapy.

Keywords
Veliparib, PARP inhibitor, solid tumor

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Introduction

With an increased understanding of the hall marks of cancer, there has been an rise in the development of target-defined antineoplastic agents. PARP is a family of proteins that play a critical role in various cellular processes like cell cycle regulation, transcription and DNA repair pathways.[1] PARP inhibitors represent a new class of drugs that is based on the concept of synthetic lethality and has shown promising results in early phase trial.[2] Veliparib, which is an investigational oral PARP inhibitor with chemosensitizing and antitumor activities is being evaluated in clinical trials for multiple tumor types.[3]

Synthetic lethality is a phenomenon whereby cell death occurs as a result of concurrent disruption of multiple genes, while a disruption in an individual gene is compatible with cell survival. The discovery of synthetic lethal interaction among PARP and BRCA1/2 was in 2005.[2] In the absence of either BRAC1 or BRAC2,PARP acts as the only backup system that can sustain the cell. Therefore, PARP inhibition has potentially lethal effects on the cell and hence veliparib was found to be particularly useful in tumors that harbour BRCA mutations.[4]

AbbVie, a global biopharmaceutical company received FDA granted orphan drug designation for Veliparib for the treatment of advanced squamous non-small cell lung cancer in November 2016.

The aim of this review is to provide an insight into the recent updates concerning the safety and efficacy of

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REVIEW ARTICLE

An Insight into the Chemistry and Pharmacological Activities of Carbazole Derivatives: A Review

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ABSTRACT

Carbazole is a heterocyclic nitrogen-containing chemical which has a versatile role in different fields of research. It has a tricyclic structure with two six-membered benzene rings joined on each side with a nitrogen-containing five-membered ring (sandwiched between two 6 membered rings). Carbazomycins and murrayafoline A are two examples of naturally occurring medicinally active compounds that contain the Carbazole ring. Compounds derived from carbazole ring are biologically potent having antitumour, antibiotic, antiviral, anti-inflammatory and neuroprotective properties. The researches done in cancer chemotherapy have suggested carbazole skeleton as a promising lead for cancer treatment. The strong cytotoxic activity elicited by carbazole can be highlighted with its polycyclic and planar aromatic structure. Topoisomerase 2 inhibition exerted by carbazole derived compounds can be employed for developing novel anticancer agents which could replace the cardiotoxic top 2 poisons available in the market.

Keywords: Carbazole derivatives, Anti microbials, Anti-HIV drugs, Anti diabetics, anti convulsants, Alzheimer's disease, Cancer, TopoisomerseII ,Diarrhoea

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RESEARCH ARTICLE

Development and Validation of a Solvent Extraction UV Spectrophotometric Method for the Estimation of Rosuvastatin Calcium and Telmisartan in Combined Dosage Form

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ABSTRACT:
A simple, precise, accurate and reproducible method has been developed and validated for the estimation of Telmisartan and Rosuvastatin Calcium in their combined tablet dosage form using solvent extraction method followed by UV spectrophotometry. The absorbance was measured at 243.8nm and 295.3nm for Rosuvastatin and Telmisartan respectively. Linearity was found over the concentration range 5-25 micro gram per ml. The solvents used for the estimation were methanol for Telmisartan and phosphate buffer for Rosuvastatin. The method was statistically validated for accuracy, precision, linearity, LOD and LOQ according to ICH guidelines and can be used for analysis of combined dosage form as well as for the individual drugs.

KEYWORDS: Telmisartan, Rosuvastatin Calcium, solvent extraction, spectrophotometric method, methanol, Phosphate Buffer.

INTRODUCTION:

Telmisartan is an angiotensin II receptor antagonist (ARB) used in the management of hypertension. It selectively antagonizes angiotensin II binding to the AT1 subtype receptors. Inhibition of AT1 receptors leads to vasodilation and inhibits the angiotensin II mediated aldosterone production which in turn leads to decrease in sodium and water excretion and also increases potassium excretion and thereby causes a reduction in blood pressure. Chemically it is 2-(4-{[4-methyl-6-(1-methyl-1H-1,3-benzodiazol-2-propyl-1H-1,3benzodiazol-1-yl] methyl} phenyl) benzoic acid.[1,2]

Rosuvastatin Calcium is chemically, (E)-(3R,5S)-7-(4-(4-flurophenyl)-6-isopropyl-2-[(methyl(methanesulfonylamino)] pyrimidine-5-yl)-3,5-dihydroxyhepten-6-oic acid calcium.

Normally statins are HMGCoA reductase inhibitors that are found to be effective in the reduction of total cholesterol and LDL cholesterol and hence it is indicated for dyslipidemias. In addition to it, rosuvastatin also possess pleiotropic effects which include improvement in endothelial function, anti-inflammatory, antithrombotic and anti-oxidant effects.[1,2]

Rosuvastatin Calcium and Telmisartan is used as fixed dose combination in the coronary heart disease. This combination contains rosuvastatin 10mg as a lipid lowering agent and Telmisartan 40mg as an antihypertensive agent. Various analytical methods are available for the estimation of Telmisartan and rosuvastatin in combined dosage form as well as individual drugs[3-13]. The aim of the present study was to develop a simple UV spectroscopic method which can be used in regular laboratory practices.[2]

MATERIAL AND METHODS:

Materials:

The pure samples of Rosuvastatin Calcium and Telmisartan were obtained as gift samples from Microlabs. The solvents used were analytical grade Methanol and Phosphate buffer pH 5.5. Marketed product TELROSE was obtained from local market.

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Article Detail

Mechanistic Approach Of Topoisomerase Ii ? Inhibitors For Anticancer Activity: A Review

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Abstract: DNA topoisomerases are able to solve topological problems resulting from replication, transcription, recombination, and reorganization of the chromatin. Topoisomerases change the state of supercoiling of the DNA and therefore, have great impact on gene activity. The topoisomerases act by transiently cutting one or both strands of the DNA. Type II topoisomerase can relax supercoiled DNA by causing double-stranded break in an ATP and Mg2+ dependent manner. Drugs like Etoposide, Doxorubicin, and Mitoxantrone inhibits both the isoforms of Top II (a and ß) and are regarded as most effective anticancer drugs. Despite the wide applications of topo II inhibitors in cancer therapy, there is still an urgent need to upgrade topo II inhibitors to cope with drug resistance and dose limiting cardiotoxicity. This review focuses on the reported Topoisomerase II a inhibitors in literature and try to analyse the interaction of these molecules with enzyme. Additionally, this study attempts to recognize the common structure features of Top II a inhibitors and correlate it with their reported effects on cell mechanisms and discuss the possibilities of developing specific novel inhibitors.

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REVIEW ARTICLE

A Review Article: Synthesis and Anticancer Activity of Coumarin Derivatives

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ABSTRACT

Cancer is the one of the most leading cause of death globally. Statistics by WHO shows that about 9.6 million deaths have been occurred in 2018. Although treatments are available for various type of cancers, serious adverse effects are drawbacks of these therapies. Coumarins are one of the key compounds in cancer therapy due to increased biological activity and less toxicity. They are commonly used for prostate cancer, renal cell carcinoma and leukaemia. In this review, we have tried to review about the anti-cancer activity of coumarin derivatives and synthesis of some of the derivatives from various research studies.

Keywords: cancer, coumarin derivatives, structure, synthesis, apoptosis

INTRODUCTION

Coumarins are benzopyrone derivatives having antitumor activity. They act by a variety of mechanisms such as carbonic anhydrase inhibition, activation of cell apoptosis protein, inhibition of tumour angiogenesis, inhibition of microtubule polymerization etc. (20) coumarins was first isolated from the plant dipteryxodorata wild belongs to family Fabaceae. Previous studies on coumarin derivatives found out that they have anti-bacterial, antifungal, anti-inflammatory and anti-HIV properties.7 hydroxycoumarin a coumarin metabolite show cytostatic activity on human cancer cell lines such as HL-60 (leukaemia) MCF-7 (breast) A549 and H727 (lung). It also have cytostatic activity against prostate tumour, metastatic kidney carcinoma.3,4 hydroxycoumarin derivatives also have antiproliferative activity on gastric carcinoma cell lines. (21)

Synthesis of Various Coumarin Derivatives

3-Acetylcoumarin

In a study synthesis of this compound was as follows; salicylaldehyde (1 eq.) with ethylacetoacetate (1eq.) with a few drops of piperidine were combined at room temperature for 5 minutes without any solvent. The reaction was neutralised with 1M HCl, afterwards the product was filtered out. In EtOH, the finished product was recrystallized

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ORIGINAL ARTICLE

Development of Green Synthesized Chitosan-coated Copper Oxide Nanocomposite Gel for Topical Delivery

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Accepted: 9 December 2022

Abstract

Purpose This research focuses on the development of a green synthesized chitosan-coated copper oxide nanocomposite gel for topical delivery. Due to the emergence of multidrug resistance and the lack of new antibiotics, bacterial infections, unintentional or otherwise, have become a serious disease that can be fatal. Under these circumstances, healthcare industries are under extreme pressure and in need of novel, multifunctional materials to combat human diseases. Nanocomposite-coated biopolymers are currently the most promising materials in the healthcare sector.

Methods The green synthesized nanocomposite was characterized using zeta potential, particle size, X-ray diffraction (XRD), UV–visible spectroscopy, and FE-SEM analysis. The broth dilution method was used to determine the minimum inhibitory concentration (MIC) of the nanocomposite against gram-positive and gram-negative bacteria. The optimized nanocomposite was used for further development of antibacterial gel using different concentrations of Carbopol, and all formulations were subjected to physical evaluation such as pH, viscosity, spreadability, and extrudability.

Results Chitosan-coated copper oxide nanoparticles (CS-CuO) showed maximum absorption in the visible region at 416 nm. The XRD data showed characteristic diffraction patterns of the phases. The FE-SEM image of the synthesized nanocomposite showed a spherical shape. The MIC was 800 µg/ml.The average *Z* value, polydispersion index, and zeta potential obtained were found to be 235.7nm, 0.777, and 15 mV, respectively. The optimized formulation showed acceptable physical properties in terms of color, homogeneity, consistency, spreadability, and pH.

Conclusion The synthesized CS-CuO nanocomposite gel has antibacterial properties and is effective for topical application.

Keywords Green synthesis · Chitosan · Copper oxide · Nanocomposite · Topical delivery

Introduction

Nanotechnology has opened up new avenues for using nanomaterials as alternative multifunctional agents to treat both microbial infections and viruses in recent decades [1, 2]. Natural organic biopolymer substituted for inorganic nanoparticles (NPs) has various advantages including low cost, improved NP stability, absence of particle agglomeration, uniform distribution of NPs, excellent photocatalytic activity, decreased metal ion toxicity, and material reuse possibilities [3–8].

Copper oxide (CuO) can be used as an inorganic biocidal agent when combined with biopolymers that exhibit antibacterial properties. The synergistic effect of the two individual materials contained in the composition would undoubtedly increase the biocidal capacity of the resulting nanomaterial [9–12]. Metallic nanoparticles such as copper are particularly important among the many nanoparticles, because they are inexpensive, widely available, and have been developed using green chemistry methods due to their affordability, environmental friendliness, and nontoxicity [13, 14].

Methods such as UV irradiation, chemical precipitation, sonication, sol–gel, and microemulsions have been used to prepare transition metal and metal oxide nanoparticles [15–21]. The use of hazardous solvents and risky chemical reducing agents such as sodium borohydride and hydrazinium hydroxide to prepare chemically generated metal oxide nanoparticles has negative environmental impacts. The precursors would attach to the extended

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RESEARCH ARTICLE

Neem Oil Versus Neem Extracts: An Approach in Comparison of Medicinal Applications

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ABSTRACT

Neem oil is a fixed oil pressed from fruits and seeds of neem and has been used in pest control due to its insecticidal and medicinal properties. Neem has antiallergenic, antidermatic, antifeedent, antifungal, anti-inflammatory, antipyorrhoeic, antiscabic properties as well as cardiac, diuretic, insecticidal, larvicidal, nematicidal, and spermic properties. Triglycerides make up neem oil, which also contains a lot of triterpenoid chemicals. Stigmasterol, terpinene-4-ol, sugiol, 4-cymene, nimbiol, -terpinene, and vitamin E are all found in neem leaf extract. Various experimental research on the antifungal properties of neem oil have been undertaken. Due to its diverse medicinal activities neem oil has been found beneficial in ayurvedic and allopathic medicine. Despite of the applications, neem oil and extracts are available in limited dosage forms. Many approaches had been used to formulate neem oil and extracts as advanced delivery systems for topical drug delivery.

Keywords: Neem oil, Neem extract, Azadiractin, Antifungal activity, Zone of inhibition

INTRODUCTION

Neem tree (*Azadirachta indica*) a fast growing tree belongs to family 'Meliaceae'is a tropical evergreen tree related to mahagony. Neem oil is a fixed oil pressed from fruits and seeds of neem and has been used in pest control due to its insecticidal and medicinal properties. Neem oil is normally yellowish- brown, golden -yellow, reddish brown, dark brown, greenish- brown or bright red liquid in colour (Figure 1). It has an unpleasantly offensive and strong odour. The oil has a smell of partial combination of peanut and garlic. For proper emulsification oil needs appropriate surfactants due to its hydrophobic nature. It is a non drying oil and its obnoxious odour is due to the presence of