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The science of resveratrol, formulation, pharmacokinetic barriers and its chemotherapeutic potential

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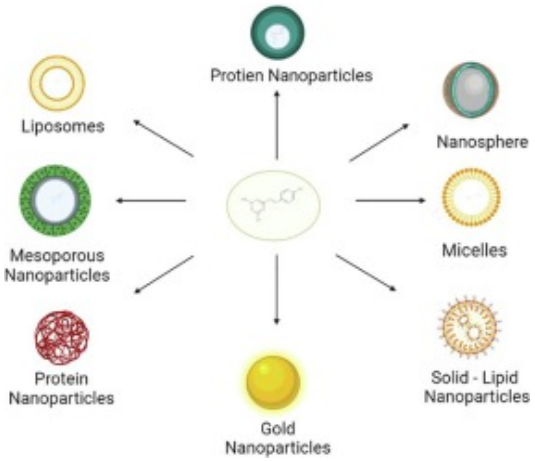
Abstract

Chemopreventive properties of resveratrol has been studied for decades. Despite its potential for chemotherapeutic advancement, the compound has pharmaceutical limitations, such as, the drug has a poor pharmacokinetic profile and low bioavailability. Studies have comforting results that that the nano-formulations may aid the future resveratrol drug development. Resveratrol can also be encapsulated as co-drug with an anticipation of gaining improved targeting and pharmacokinetic parameters, as well as achieving desired therapeutic plasma levels. It has been envisaged that the nanoformulations can also address the issue of drug accumulation, which may lead to hepatotoxicity. Nanoformulations can bring a major improvement in the bioavailability of resveratrol but still the formulation still suffers with pharmacokinetics issues clinically. This review encompasses the pharmacokinetics barriers associated with resveratrol and a possible suggestion to overcome those barriers for improving absorbance, reducing toxicity and improving the drug release and encapsulation efficiency. The article also suggest that co-administration of resveratrol with chemotherapeutic drugs must be tested *in vivo* on a wide range of cancers to avoid accidental proliferation exacerbation. The review's focusses on the resveratrol formulation and make suggestions for improvements in order to overcome the pharmacokinetic and toxicity issues.

Graphical abstract



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Introduction

Over the last several decades, the economic and health burden that cancer imposes on the world has ceased to decline. There has been significant rise in cancer cases and mostly it has been associated to the changed life style. Obesity and tobacco use have worsened the situation and are now considered among the leading risk factors in the UK. Despite the fact that the cancer survival rate has doubled in the last four decades, cancer remained responsible for more than one in every four deaths in the United Kingdom in 2017, thus highlighting the urgent need for therapeutic advances (UK, 2021). Personalised medicines have been at the forefront of the development of new anti-cancer therapeutics that have proven to be successful. Recently developed gene testing techniques are also crucial to finding new cancer drug targets. Shuford *et al.* illustrated this by examining the RAS oncogene family in colorectal cancer, wherein they found, it is frequently found overexpressed in many cancers. Cancer environments, including the pathways that are overexpressed, have also been tailored to personalise successful treatments (Das et al., 2020, Gracia-Sancho and Salvadó, 2017, Shuford et al., 2020). Despite advances in therapeutics, the prognosis for cancer patients remains grim, with only one out of every two patients living for ten years. Barriers such as infinitely changing tumour microenvironments and mutations (Maeda and Khatami, 2018), heterogeneity of cancer DNA, and obstacles in cancer target identification (Shuford et al., 2020) have hampered high success rates in therapeutic remissions, despite the development of individualised treatments. Surgery, radiotherapy, and chemotherapy are the three main cancer treatments available today. Most chemotherapeutics have toxic side effects and non-selective cell destruction, hence necessitating the development of new therapeutic options (Pérez-Herrero and Fernández-Medarde, 2015).

With over 200 new compounds identified in the last 50years, natural compounds have become a massive area of research for future lead compounds in chemotherapeutics. Resveratrol exploration is clinically important and a current area of research following the success of discovering new therapeutics from natural compounds, such as Etoposide (Agarwal et al., 2020). Resveratrol, a polyphenol is a natural compound found in over 70 food sources (Jang, 1997), such as berries, grapes, peanuts and red wine. Although this is a dietary compound, the levels found in such foods are not high, with less than 1.8mg/mL of resveratrol found in red wine (Xiao et al., 2019). Historically, the polyphenol has been extracted under thermal conditions followed by ethanol refluxing. Newer cost viable methods, such as high-speed counter current chromatography are being explored to aid *trans*-resveratrol identification, (Gao et al., 2016).

Resveratrol is a polyphenolic stilbene with a double bond connecting the 2 phenol rings, which exists as a white powder The bond allows for geometric isomerisation via UV irradiation (Chen et al., 2007). The *trans*-isomer besides being more biologically active, is also more abundant than the cis isomer (Fig 1).

Resveratrol's potent biological activity has been widely recognised, encompassing numerous medicinal properties, including inflammation mediation, cardio protection, anti-oxidizing properties, antiviral and antifungal properties, and phytoalexin activity. The anti-neoplastic activity of resveratrol is also widely reported (Rauf et al., 2017, Xiao et al., 2019). Resveratrol has been studied for its potential anti-cancer effects in the three stages of cancer development: tumour cell initiation, promotion, and progression. The anti-neoplastic effects of resveratrol are thought to be due to a variety of biological mechanisms. Inhibition of the tyrosine kinase epidermal growth factor receptor pathway is one of the reported pathways that disrupts important pro-carcinogenic signalling pathways. This inhibits kinase activity, preventing the uncontrolled cell proliferation seen in cancer cells (Jang, 1997, Varoni et al., 2016). Resveratrol is also thought to activate onco-surveillance via tumour suppressor cells and apoptosis, and prevent angiogenesis (Xiao et al., 2019), among other mechanisms (Rauf et al., 2017) (Fig. 2).

The review focuses on the anti-oxidant and pro-oxidant properties, as well as the pharmacokinetic issues associated with resveratrol. It also underlines the use of resveratrol nanoparticles prepared using inorganic nanoparticle materials and proteins such as zein, casein, etc. for medical purposes. The review also encompasses the synergistic effects of resveratrol with metal ions such as gold, silver, copper, zinc, and polyherbal formulations containing curcumin, quercetin, quercetin and genistein, and chemotherapeutic substances such as docetaxel and sulfasalazine. It highlights the existing research gaps as it focuses on the literature from the last 5 years.

Before it can be considered clinically useful in chemotherapeutics, resveratrol must overcome numerous pharmacokinetic hurdles. The low bioavailability is a significant issue, despite the fact that it is well absorbed when taken orally, with a bioavailability of around 70%. It has been reduced to a 5% systemic availability. This is due to extensive metabolism in the liver and intestines, including glucuronidation and sulfation, which produces metabolites with lower biological activity than resveratrol. Further, trans to cis conversion could be attributed to air oxidation, light, oxidative enzymes, and high temperatures (Peñalva et al., 2018, Wang et al., 2020). Compounding more to the problem is resveratrol low water solubility, which is around 0.03 mg/mL, hence affecting the compound's absorption and bioavailability (Wang et al., 2020).

Newer delivery system are currently being investigated to overcome these pharmacokinetic barriers and improve resveratrol bioavailability. Nano-formulations appears to be a promising option as they could possibly prevent drug degradation besides improving solubility and controlling drug release kinetics. Metal-based deliveries, compound derivatives, and polyherbal formulations are among the other formulation areas being researched. The present review highlights the chemo-preventive potential and pharmacokinetic profile of resveratrol in different formulations, to assess if formulations could be a resolution to the bioavailability issues of resveratrol.

As discussed above, resveratrol has a poor pharmacokinetic profile and of the few reasons, this could be further attributed to rapid enteric and hepatic metabolism, as well as a high percentage of first-pass drug elimination Besides these limitations there is a growing evidence supporting its potential chemo-preventive mechanisms (Vijayakumar et al., 2016a). An examination of two weeks human urine samples after taking 1 g *trans*-resveratrol suggested that resveratrol was quickly metabolised to sulphate and glucuronide conjugates and excreted in the urine (Honari et al., 2019, Radko et al., 2013). Similarly, analysis for resveratrol concentrations in patients receiving5mg/1g oral resveratrol up to 2 weeks before a prostate biopsy revealed

low levels of resveratrol but a high levels of glucuronide and sulfate metabolites (Cai et al., 2021). Bioavailability was not heavily accounted for in this study, and the *in vivo* translation to humans would be limited due to the extensive pharmacokinetic downfalls of resveratrol. The evidence for enterohepatic recirculation also proves resveratrol's extensive metabolism. A study on healthy volunteers, who either consumed 500 mg of powder containing resveratrol or a micellar formulation of resveratrol, showed that, when their plasma and urine levels were tested over a 24-hour period, the plasma levels were seen to peak and again at around 8 h- suggesting recirculated metabolism (Calvo-Castro et al., 2018, Singh and Pai, 2014).

Resveratrol's bioavailability is currently the rate-limiting factor in oral efficacy due to extensive metabolism and elimination, as well as poor aqueous solubility. Calvo *et al.*. found only 2% of orally consumed resveratrol in urine samples collected after 12 h of feed, the supporting data suggested oral bioavailability was as low as 5% (Calvo-Castro et al., 2018). Resveratrol appears to have the same bioavailability when used in gelatine capsules, with water as a control, or when used with dairy/protein co-administration. This study recognised its limitations and suggested complex meals may improve resveratrol bioavailability than isolated food groups (Draijer et al., 2016). Multiple studies have found that resveratrol has low oral bioavailability and is unstable in the environment due to factors like oxidation and photosensitivity. A study found larger oral doses may produce mild physiological benefits but obtaining this dose in is not feasible (Honari et al., 2019, Jhaveri et al., 2018, Smoliga and Blanchard, 2014). The oral bioavailability of resveratrol varies from person to person. However, the implications for cancer patients in particular need to be investigated further, and this indicates towards a significant research gap. Cancer is a metabolic disease, so the concern of altered metabolism on the already complex and sometimes opposing biological mechanisms of resveratrol could lead to very different therapeutic efficacy (Risuleo, 2016).
Resveratrol has been found to exert its anti-neoplastic effects through multiple biological mechanisms leading to both chemo-preventive and chemo-protective qualities. Studies have reported that the antioxidant activity of resveratrol promotes production of nitrous oxide and thus inhibiting oxidative stress. It may also prevent cell proliferation, apoptosis, arrest cell cycle of tumour cells and inhibit gene phosphorylation (Cocetta et al., 2021, García-Quiroz et al., 2019, Honari et al., 2019, Jhaveri et al., 2018, Liang et al., 1999, Mirzapur et al., 2018, Monteillier et al., 2018, Qin et al., 2020, Sonnemann et al., 2015). Resveratrol has the ability to prevent oxidative stress, and thus limits cell proliferation and mutation (Ozben, 2007). The antioxidant properties of resveratrol have been listed in the literature (Honari et al., 2019, Jang, 1997), However, in the presence of resveratrol and copper ions, DNA mutations appeared to be potentially pro-oxidant (Ahmad et al., 2005). Pro-oxidant properties were further emphasized when melanoma cells were cultured with resveratrol and assayed for concentrations of reactive oxygen species (ROS). Despite increased reactive oxygen species, cell death increased by 15-fold with 10 μm resveratrol compared to the control (Heo et al., 2018). This suggests both redox potentials played an important role in resveratrol's anti-neoplastic mechanisms.

Resveratrol is known to trigger autophagy, a complex anti-neoplastic mechanism involving proteins and lipids that are broken down, and then used by auto phagosomes (Lamy et al., 2013, Lang et al., 2015). Resveratrol has also been shown to increase autophagy and apoptosis in glioma cells. During fluorescence examination after resveratrol treatment, Beclin-1, an autophagic protein, was also measured in hepatocellular carcinoma cells (Lang et al., 2015, Zhang et al., 2018). Increased expression of autophagic genes Atg12 and Atg7 was confirmed in a resveratrol treated hepatoma cell line resulting in increased apoptosis (Liao et al., 2010). However, Autophagy can have controversial effects in cancerous microenvironments, and can inhibit the death of tumour cells under nutritional deprivation, which can occur in cancer. The synergism of resveratrol with another natural compound- Quercetin was also found to decrease autophagic effects, suggesting this mechanism is unpredictable and sensitive (Tomas-Hernández et

al., 2018). Further evidence has shown melanoma cells require basal levels of autophagy to remain proliferative (Lamy et al., 2013).

Resveratrol is a phytoestrogen and naturally has a blend of anti/pro-estrogenic effects (Salehi et al., 2018). Resveratrol has been shown to have oestrogen receptor -α (ERα) mixed antagonist activity but not ER-β. As a result, cancers with high ER expression are more likely to proliferate when exposed to resveratrol. It can however have potent anti-estrogenic properties, particularly in ER-rich tumours, as evidenced by breast cancer studies (Cocetta et al., 2021, Mirzapur et al., 2018). More understanding is needed on the effect the tumour microenvironment (including other metal ions), and other factors such as age has on resveratrol's mechanisms. Resveratrol shows capability to work in opposing ways, so triggers for pathways should be explored in future research.

The data on humans are encouraging, but a lot is based on *in vivo* animal research, that cannot be transferred to human pharmacokinetics. Although *in vitro* data is useful for extracting and analysing specific mechanisms and cells, *in vivo* data would support more human clinical trials and regulatory approval, since now we have a better understanding of resveratrol's mechanisms. Chen *et al.* provided growing evidence for *in vivo* anti-neoplastic effects with an induced renal carcinoma study on mice. It was deduced that resveratrol may help inhibit renal tumours in a dose-dependent manner (Chen et al., 2015). In contrast, a study on hairless mice with induced skin carcinoma found no statistical evidence that dietary grape powder containing resveratrol-reduced carcinogenesis (Singh et al., 2019).

Section snippets

Pharmacophoric approaches and limitations

Solubilization of the molecule, which is often accomplished through small structural changes, is the first logical area of resveratrol formulation research in order to improve bioavailability. This may include derivatives or metabolites. Resveratrol derivative synthesis, and then further metabolism, led to the study of their biological effects. The metabolites produced, were found to have stronger anti-proliferative effects than the parent compound. Molecule, I and II (Fig. 3) were most…

Conclusion

Resveratrol appears to have chemotherapeutic potential but number of issues still needs to be addressed. In addition to the complexity of a variety of chemo-preventive mechanisms, there are significant pharmacokinetic barriers. Resveratrol has been studied in a variety of ways, including, in different formulations and in combination with other compounds. Despite the fact that this field of research is newer, the potential for greater success with these formulations has been identified. There is …

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.…

Acknowledgement

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2023, Phytomedicine

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> …PTEN (phosphatase and tensin homolog deleted on chromosome 10) is regarded as a new tumor suppressor regulated by NHERF-1, whose deficiency drives M2-like polarization of macrophages in TME by increasing CCL2 and VEGF-A (Li et al., 2015). CCL2 and IL-6 recruit monocytes to TME and increases their polarization into M2 macrophages by inhibiting caspase-8 cleavage and enhancing autophagy in macrophages(Roca et al., 2009). S100 calcium-binding protein A9 (S100A9) is an inflammatory microenvironment-related secretory protein up-regulated in TAMs and acts on tumor cells through AGER/NF-κB axis, thereby facilitating the transcription of CCL2, which accelerates the expression of S100A9 in macrophages in return(Wei et al., 2021)….

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> …Resveratrol (RES), a natural stilbene (Fig. 1) found in grapes, blueberries, raspberries, blackberries, red wine, and chocolate, is among the most important and studied phenolic compounds (Kotta, Mubarak Aldawsari, Badr-Eldin, Alhakamy, & Md, 2021; Robertson et al., 2022)….

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