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Effects of berberine, curcumin, resveratrol alone and in combination with chemotherapeutic drugs and signal transduction inhibitors on cancer cells—Power of nutraceuticals

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ABSTRACT

Over the past fifty years, society has become aware of the importance of a healthy diet in terms of human fitness and longevity. More recently, the concept of the beneficial effects of certain components of our diet and other compounds, that are consumed often by different cultures in various parts of the world, has become apparent. These "healthy" components of our diet are often referred to as nutraceuticals and they can prevent/suppress: aging, bacterial, fungal and viral infections, diabetes, inflammation, metabolic disorders and cardiovascular diseases and have other health-enhancing effects. Moreover, they are now often being investigated because of their anti-cancer properties/potentials. Understanding the effects of various natural products on cancer cells may enhance their usage as anti-proliferative agents which may be beneficial for many health problems. In this manuscript, we discuss and demonstrate how certain nutraceuticals may enhance other anti-cancer drugs to suppress proliferation of cancer cells.

1. Introduction

Berberine (BBR), curcumin (CUR) and resveratrol (RES) are examples of three commonly consumed nutraceuticals which have been investigated for prevention/treatment of various diseases and ailments for centuries (McCubrey et al., 2017a, 2017b). These and

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other nutraceuticals are contained in different components of our diet, such as; fruits, berries, grapes, spices obtained from plants such as turmeric, oils from plants and fish and in addition leaves from various plants and trees. In general, they are not toxic at doses that we consume normally. Moreover, they have been associated with long life and the prevention of common health problems such as: cardiovascular, bacterial, fungal and viral infections, diabetes, inflammation and even obesity. There are many other nutraceuticals. Other commonly consumed nutraceuticals are olive oil and fish oil. More recently they have been investigated for their anti-cancer and anti-aging effects, two processes which are often intimately related (Cusimano et al., 2017).

Nutraceuticals can affect neurological processes. It turns out that signaling pathways are dysregulated in neurological diseases such as: Alzheimer's disease (AD), Amyotrophic lateral sclerosis (ALS) and others (Tomita, 2017; Bradshaw et al., 2015; Shamseddine et al., 2015; Tu-Sekine et al., 2015; Aditi et al., 2016; Rohacs, 2016; Giudici et al., 2016; Yang et al., 2016; Kang et al., 2016; Hayashi et al., 2016 Scarlata et al., 2016; Ghim et al., 2016; Raben and Barber, 2017). The PI3K/PTEN/Akt/mTORC1/GSK-3 signaling pathway is often regulated by nutraceuticals and it plays critical roles in: diabetes, cardiovascular diseases, inflammation, neurology, obesity, as well as cancer (Lupieri et al., 2015; Guidetti et al., 2015; Beretta et al., 2015; Mikoshiba, 2015; Huang and Natarajan, 2015; McCubrey et al., 2017c, 2017d,; Carman and Han, 2017; Hermida et al., 2017; Gowda et al., 2017a,b; Nishida et al., 2017; Ricciardi et al., 2017; Ruvolo, 2017; Ruzzene et al., 2017; Hatch et al., 2017; Yamauchi et al., 2017; Shears et al., 2017; Ramazzotti et al., 2017; Schrock et al., 2017; McCubrey et al., 2017c; Coant et al., 2017; Ebenezer et al., 2017; Mérida et al., 2017; Gowda et al., 2017a,b; Campa and Hirsch, 2017; Ryuno et al., 2017). One of the first and most effective drugs to treat certain neurological diseases is lithium which is often administered to manic depressive patients. A target of lithium is GSK-3 which is a key component of the PI3K/PTEN/AKT/mTORC1/GSK-3, WNT-beta-catenin pathways and others (McCubrey et al., 2017a, 2017b).

BBRs are contained in many plants and fruits including: *Berberis aetnensis C. Presl.*, *Berberis aristata*, *Berberis vulgaris*, *Coptis chinensis*, *Coptis japonica*, *Coptis rhizome*, *Hydrastis canadensis*, *Phellondendron amurense* and *Tinosora cordifolia*. BBR is an isoquinoline quaternary alkaloid (a 5,6-dihydrodibenzo [a,g]quinolizinium derivative). The health promoting effects of BBR has been known for centuries. BBR is often used in traditional Chinese and Indian medicine and is frequently consumed.

BBR, like CUR and RES, are sometimes considered dietary supplement. However, certain fruits containing BBR can be purchased over the counter at many different types of stores. BBR is also consumed for alleviation of various conditions/diseases such as: abdominal pain, coronary artery disease, diabetes, diarrhea, fatty liver disease, gastroenteritis, hyperlipidemia, hypertension, metabolic syndrome, neurodegeneration, obesity, polycystic ovary syndrome (McCubrey et al., 2017a, 2017b, 2017c; McCubrey and Cocco, 2017) BBR is being examined in at least 35 clinical trials.

A new aspect of BBR may be in the treatment of certain cancers. BBR is believed to have anti-diabetic, anti-inflammatory and anti-microbial (both anti-bacterial and anti-fungal) properties. BBRs can influence the expression of various genes that are involved in: apoptosis, autophagy, metastasis and proliferation such as: BCL2, BCLXL, PARP1, Beclin-1, TP53, $p21^{Cip1}$, MMP9 (Cordell et al., 2001; Tillhon et al., 2012). In addition, BBRs may induce double strand DNA breaks and cell cycle arrest (Wang et al., 2012). These properties of BBR may be related to its potential anti-cancer effects.

BBRs may interact with DNA and RNA via the nitrogen atom at the 7-positon in the alkaloid BBR skeleton. This interaction between BBR and nucleic acids may inhibit telomerases and topoisomerases (Qin et al., 2007; Kim et al., 1998; Gatto et al., 1996; Bhowmik et al., 2012). In addition, BBRs may influence gene transcription by interacting with the TATA-binding protein and the TATA-box present in certain promoter regions (*e.g.*, BCL2) (Xiao et al., 2012; Wang et al., 2011).

Some of the potential anti-diabetic and anti-cancer effects of BBRs are their ability to localize to the mitochondria and inhibit the electron transport chain and activate 5′ AMP-activated protein kinase (AMPK) and suppress mTOR activity (Wang et al., 2010a; Liu et al., 2011). The PI3K/PTEN/Akt/mTORC1 and Raf/MEK/ERK pathways are inhibited when AMPK is activated.

BBR can also inhibit senescence by altering gero-conversion from the process of cell cycle arrest to the induction of senescence by targeting mTOR/S6 and the generation of ROS (Zhao et al., 2013; Halicka et al., 2012).

The nutraceutical CUR is frequently obtained as an extract from the plant *Curcuma longa* (Turmeric). However, there are other compounds present in the extract which are referred to as curcuminoids. The turmeric extract consists of 60–70% CUR, 20–27% demethooxycurcumin and 10–15% bisdemethoxycurcumin (Nelson et al., 2017). These curcuminoid comprise 1–6% of the total weight of the turmeric tuber.

CUR is believed to have many health promoting properties including: anti-aging, anti-cancer, anti-hypertensive, anti-inflammatory and anti-neurological activities. The market for CUR is thought to be close to $100 million by 2022 (http://www.grandviewresearch.com/industry-analysis/turmeric-extract-curcumin-market). The effects of CUR are being examined in at least 129 clinical trials for various diseases.

CUR may exert some of its effects by altering drug transporter activity in cancer cells. CUR could enhance the anti-tumor properties of the DNA cross linking agent mitomycin C by inhibiting the expression of ATP-binding cassette transporter G2 (ABCG2, a.k.a breast cancer resistance protein, BCRP) expression. CUR treatment also increased the sensitivity of MCF-7 and MDA-MB-231 breast cancer cells to multiple chemotherapeutic drugs including: cisplatin, doxorubicin and paclitaxel and inhibited the sphere forming capacity of the cells when both CUR and a chemotherapeutic drug were added together. These events were shown to be dependent upon the suppression of ABCG2 by CUR treatment (Zhou et al., 2015a).

CUR has been shown to have effects on microRNA (miR) expression. CUR treatment of cutaneous T-cell lymphoma (CTCL) inhibited JAK-3 activity and induced miR-22 expression and suppressed the expression of many genes including: cyclin dependent kinase 2 (CDK2), histone deacetylase 6 (HDAC6), MYC associated factor X (MAX), MYC binding protein (MYCBP), nuclear receptor coactivator 1 (NCOA1), and PTEN. (Sibbesen et al., 2015).

An additional miR that is regulated by CUR is miR-34. CUR and miR-34 will regulate the expression of histone modifying enzymes. Histone modifying enzymes can affect the accessibility of promoter regions to transcription factors (Tao et al., 2013).