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Synergistic Interaction Between Combination of Existing Therapy with Polyphenols in Several Human Diseases: A Review

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ABSTRACT

Introduction: The complicated pathology of current diseases requires an intricate treatment. Today, current application of individual single-target drugs or therapeutic approaches is inadequate to target these diseases not to mentioned perceived shortcomings and presented with numerous adverse effects. The extensive and successful documented findings in natural product researches urges the need to make use of these knowledge in the development of new generation of medicine. Polyphenols are compounds naturally derived from plants and have been describe in many research to have tremendous medical benefit. Therefore, a synergistic combination of readily available drugs or other therapeutic approaches is a favourable approach to enhance efficacy, overcome toxicity and optimize safety. The objective of this review is to describe the synergistic effects between the combination of a variety of polyphenols with synthetic drugs or other therapeutic approaches which can help to improve therapeutic efficacy subsequently minimize the adverse effects of a substance targeted in various diseases focusing mainly on cancer, diabetic, microbial infections and tissue regeneration along with their underlying mechanism.

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Introduction

Natural products from plants have been widely applied by humans for the past centuries for treatment of various diseases (Firenzuoli & Gori, 2007). The use of natural products for medicinal purpose were being practiced by about 75% to 80% of the world population mainly because of its cultural acceptability as well as superiorly compatibility with human body (Set et al., 2010). Contrary to synthetic drugs which typically are chemically isolated compound, natural products consist of multicomponent of phytoconstituents (Ginsburg & Deharo, 2011). There are numerous elements that influence the efficacy mechanism of natural products which includes the geographical origin, plant parts (leaves, stem, root, and fruit), storage, processing, extraction as well as types of solvents used (Doughari, 2012; S.-Y. Pan et al., 2013). Over the recent years, researchers are currently focusing on natural products for drug discovery targeted for various diseases.

In spite of the facts that the process of drug discovery is now moving forward resulting in advancement of various technology platforms, drug development remains a considerable long process with a low rate of success and large investment. It takes up to years for a newly discovered chemically synthetic compound to become a successful marketable therapeutic agent (Barden & Weaver, 2010). Not to mention, readily available synthetic drug usually perceived shortcomings and presented with numerous adverse effects (Pöch, 2012). Today, thanks to scientists over the world, approximately 80% of antimicrobial, cardiovascular, immunosuppressive, and anticancer drugs are from plant origin or developed from a natural compound (Krief et al., 2004). Polyphenols are one of the natural products that has been extensively researched upon and has been described successfully either *in vitro* (Curti et al., 2017; H. Sun et al., 2018); *in vivo* (Kujawska & Jodynis-Liebert, 2018; Wang et al., 2017) or in clinical trial (Borges et al., 2016; Wauquier et al., 2019) to effectively target various disease documented with low toxicity and minimum adverse effects to human (Cory et al., 2018; Edwards et al., 2012; Nash et al., 2018).

Throughout recent years, more attention have been given by researcher to study the potential interaction between synthetic drugs with natural product targeting diverse type of diseases (Lehár et al., 2009). Thus, with the presence of recent technological advancement and abundant discovery on the effects of natural product and its health benefits; the development of a new generation medicine can be expedited by combining natural products with synthetic drugs or other therapeutic approaches (Pan et al., 2013). The potential benefits that can be gained from interaction of natural product with synthetic drug or other recent therapeutic approaches includes increased efficiency, reduction of undesirable effects increase in bioavailability of the free agents as well as gaining sufficient therapeutic effect with relatively small doses in comparison with a synthetic medication (Chanda & Rakholiya, 2011). The focal point of this review is on the discovery of synergistic effect of combination of naturally derived polyphenols with synthetic drugs or other therapeutic approaches on various diseases and medical discoveries.

The medicinal role of Polyphenols

Polyphenols represent a group of common phytochemicals that are structurally characterized by the presence of one or more phenol units which includes hydroxybenzoic acids, hydroxycinnamic acids, anthocyanins, proanthocyanidins, flavonols, flavones, flavanols, flavanones, isoflavones, stilbenes, and lignans (Gupta et al., 2008) . Flavonoids for example can be further subdivided into flavones, flavonols, flavanones, isoflavones, anthocyanidins, chalcones, and catechins predominantly found in fruits, vegetables, legumes, red wine, and green tea and have a potential effect on radical scavenging activity and inflammatory reactions (Xiao et al., 2011). Additionally, stilbenes or resveratrol are polyphenols found in product of grapes, red wine, and peanuts. Meanwhile, phenolic acids found in coffee, tea, cinnamon, blueberries, kiwis, plums, apples, and cherries; all has been reported to elicit tremendous health benefits (Hasan et al., 2013; Sales & Resurreccion, 2014).

It has been documented that different groups of polyphenols have shown to have different biochemical mechanism and acts differently in response to various modes of diseases. Numerous studies confirm that treatment by using variety of polyphenolic compounds either single compounds or in groups as well as dietary intake of natural sources rich in polyphenols, reduced incidence of chronic diseases. Polyphenols mainly acts by interacting with reactive oxygen species (ROS). ROS are typically formed within human body in a controlled amount and are vital compounds that are related in the regulation of processes in maintaining cell homeostasis and functions such as signal transduction, gene expression, and activation of various signaling receptors (Kumar & Pandey, 2015). The involvement of polyphenols on ROS has suggested to be associated with the etiological effects on prevention of different disease pathologies (Lima et al, 2014).

Tremendous researches have shown the therapeutic potential of polyphenols (Figure 1)(Ganesan & Xu, 2017) such as anti-diabetic (Cao et al., 2017), anticancer (Devi et al., 2017), anti-inflammatory (Yahfouf et al., 2018), cardioprotective (Arbeláez et al., 2018), osteoprotective (Brzóska et al., 2016), neuroprotective, antiasthmatic, antihypertensive, antiageing, antiseptic, hepatoprotective, antifungal,

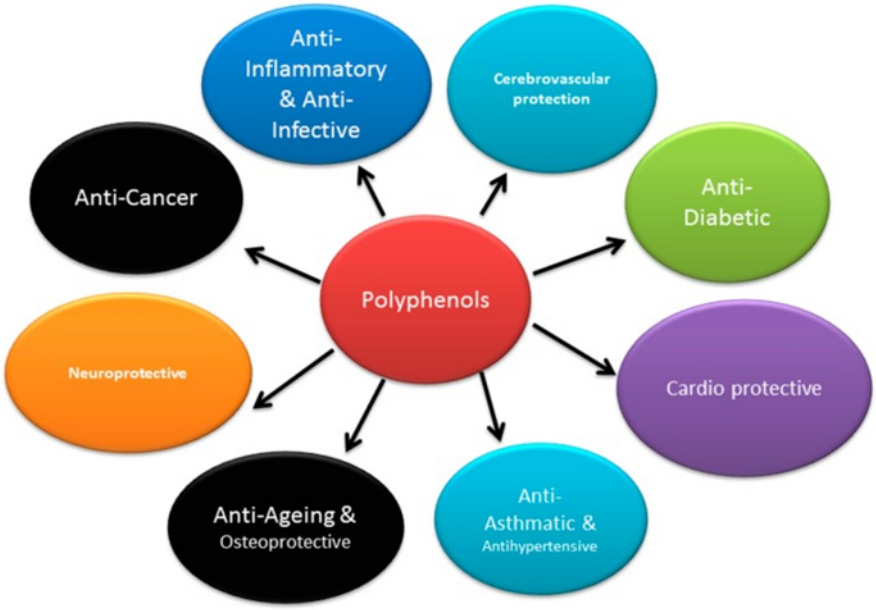

Figure 1: Role of polyphenols in humans (Ganesan & Xu, 2017)

antibacterial and antiviral properties (Ganesan & Xu, 2017; Gorzynik-Debicka et al., 2018; Gupta et al., 2008).

Synergistic mechanism

Development of combined pharmaceuticals or therapeutics substances primarily aimed to achieve synergism in order to remain clinically significant. Researcher has denoted how latest molecular biological methods and new genomic technologies allow us to unwinds the various synergistic mechanisms underlying these effects (David et al, 2015). However, recognition of successful drug combination is complicated and often remains a setback due to lack of standardization in the aspect of terminology, experimental protocols as well as drug modelling.

Synergistic effects are produced when compounds interact with one another of the same constituents or in combination with other compounds such as synthetic drugs, biomaterials and other therapeutics approaches. The mechanism of synergy will effect different targets in order to improve the solubility and by that means enhance the bioavailability of one or several substances of a compounds (Pöch, 2012). The general standardized method used to measure synergisms and antagonisms is the isobologram method in which concludes the iso-dose effect of two or more substance acting together (Berenbaum, 1989). Moreover, the construction of a dose response curve also allows investigation of combined effects of investigated compounds (Chou, 2006). Additionally, to achieved a successful combined therapy synergism it is important to also consider numerous factors affecting drug-drug interactions or compounds interactions (natural products) such as compound target site, affected pathway of compound, process or pathogenesis the compounds acts on and most importantly patients' ability to absorb, metabolize and excretes a substance or compounds (Pemovska et al., 2018; X. Sun et al., 2013).

Methodology

The relevant articles were searched through PubMed, Google Scholar and ScienceDirect database. The following keywords and search terms were used: "synergistic combination of polyphenols therapy" in "anti-cancer", "anti-microbial", "anti-diabetic," "cardio-protective" and "regenerative effect". The articles were screened and the articles that are related to the search keywords dated from the year from 2000 to 2020 were included in the review.

Results

Synergistic interaction between combination of existing therapy with polyphenols on various diseases

Over the recent years, consistent efforts have been made to translate the benefits offered by natural product into clinically relevant substances or therapy in many diseases setting. In this review, we listed the successful work of the combination treatment; by employing existing standardized therapy such as synthetic drugs and biomaterials commonly used in clinical setting with polyphenols (Table 1) and its mechanism. In most cases, transforming experimental research for clinical based trial might be hard, however, in combination therapy; through the use of existing standardize regimes and protocol; polyphenols can simply be introduced safely in clinical trials for example through diet or in the form of

Table 1: Therapeutic combination of existing therapy with polyphenol on various diseases target.

Drugs or therapeutics approach	Polyphenols	Targets	Experimental models	Experimental findings	Ref
Anticancer					
Tamoxifen	Green tea extract	Breast cancer	*In vitro* MCF-7, ZR75, T47D breast cancer cell line and *in vivo* breast cancer induced mice model	i. *In vitro* green tea extract increased the inhibitory effect of tamoxifen on the proliferation of estrogen receptor (ER) -positive MCF-7, ZR75, T47D human breast cancer cells. ii. *In vivo* mice treated with both green tea and tamoxifen showed highest apoptosis in tumor tissue compared with either agent administered alone.	(Sartippour et al., 2006)
Trastuzumab	Oleuropein aglycone from extra virgin olive oil extract	Breast cancer	*In vitro* SKBR3 breast cancer cell line	Increased efficacy of trastuzumab in the presence of oleuropein aglycone via significant reduction of HER2 gene; that are associated with unfavorable breast cancer prognosis includes high fatality and relapse rate.	(Menendez et al., 2007)
Docetaxel	Curcumin	Breast cancer	Phase I clinical trial on advanced metastatic breast cancer patients	Fourteen patients were accrued in the trial. Findings showed combination dose of curcumin for seven consecutive days every 3 weeks with a standard dose of docetaxel improved biological response and clinical presentation in most patients indicated encouraging efficacy results.	(Bayet-Robert et al., 2010)
Doxorubicin (DOX)	Quercetin	Breast cancer	*In vivo* mice model transplanted with 4T1 breast cancer cells.	Combination of dietary quercetin with intratumoral DOX injection synergistically induced potent rejection of 4T1 breast cancer, induced T-cell tumor specific response that results in long-term, tumor-free survival in mice.	(Du et al., 2010)
Doxorubicin (DOX)	Silymarin (SLM) from seeds of Silybum Marianum	Breast cancer	*In vitro* 4TI breast cancer cell line	Combination of SLM-DOX exerts synergistic growth inhibitory effects on 4TI breast cancer cell line.	(Gheybi et al., 2019)

Table 1 (cont.): Therapeutic combination of existing therapy with polyphenol on various diseases target.

Drugs or therapeutics approach	Polyphenols	Targets	Experimental models	Experimental findings	Ref
Doxorubicin (DOX)	Epicatechin gallate (ECG) and epigallocatechin gallate (EGCG) from green tea extract	Liver cancer	*In vitro* human hepatocellular carcinoma (HCC) cell line; BEL-7404 and BEL-7404/DOX and *in vivo* mice model transplanted with BEL-7404/DOX HCC cells.	ECG and EGCG increased chemosensitivity to DOX and increase DOX cytotoxicity in BEL-7404/DOX cells by inhibiting P-gp pump function that contribute to the reversal of multidrug resistance (MDR) *in vitro* and *in vivo*.	(Liang et al., 2010)
SAHA-suberoylanilidine hydroxamic acid Zolinza (vorinostat)	epigallocatechin-3-gallate (EGCG) from green tea extracts	Melanoma	*In vitro* A-375, Hs-294T and G-361, human melanoma cell line.	Combination treatment EGCG with varinostat resulted in significantly higher inhibition of cell proliferation, increased apoptosis via modulation of the cyclin-cdk-cki network, Bcl2 family proteins and NF-κB activity.	(Niha et al., 2010)
Cisplatin	Theaflavin (TF) and epigallocatechin-3-gallate (EGCG) encapsulated in biodegradable nanoparticulate (TF/EGCG-NPs)	Lung cancer, acute monocytic leukemia (AML) and cervical cancer	*In vitro* A549 human lung adenocarcinoma cell line, THP-1 human acute monocytic leukemia cell, HeLa human epithelial cervical cancer and *in vivo* ascites carcinoma induced mice.	Combination of TF/EGCG-NPs with cisplatin inhibited NF-κB activation and suppressed cyclin D1 activation, matrix metalloproteinase-9, and vascular endothelial growth factor (VEGF), involved in cell proliferation, metastasis, and angiogenesis *in vitro*. *In vivo* findings showed that combination treatment increased the life span of mice model with apparent regression of tumor volume compared to either agent alone.	(Singh et al., 2015)
Leptomycin B (LMB)	Epigallocatechin-3-gallate (EGCG)	Lung cancer	*In vitro* A549 human lung adenocarcinoma cell line	Combination treatment of EGCG enhanced LMB cytotoxicity through enhanced ROS production and modulation of drug metabolism via p21/survivin pathways.	(Cromie & Gao, 2015)
Doxorubicin (DOX) and etoposide	Quercetin, apigenin, emodin, rhein and cis-stilbene (commercial compounds)	Lymphoid and myeloid leukemia	*In vitro* TIB-152 peripheral blood T cell leukemia, CCRF-CEM acute lymphoblastic leukemia, THP-1 acute monocytic leukemia and KG-1a acute myelogenous leukemia	DOX alone combined with quercetin, apigenin, emodin, and cis-stilbene synergistically leads to the downregulation of glutathione and increased apoptosis via caspase 8 and 9 activation in myeloid leukemia.	(Mahbub et al., 2015)

Table 1 (cont.).: Therapeutic combination of existing therapy with polyphenol on various diseases target.

Drugs or therapeutics approach	Polyphenols	Targets	Experimental models	Experimental findings	Ref
Bleomycin (BLM)	Tea polyphenols (TPP)	Antioxidant based therapy for cervical cancer	*In vitro* SiHa cervical cancer cell line	The TPP-BLM treatment synergistically induced apoptosis through caspase-3, caspase-8 and caspase-9 activation, Bcl-2 upregulation and p53 overexpression as well as increased the percentage of apoptotic nuclei in nuclear staining.	(Alshatw et al., 2016)
Tamoxifen (TAM)	Genistein (soy-based extracts)	Hepatocellular carcinoma	*In vitro* HePE2 human hepatocellular carcinoma cell line	Genistein and TAM significantly inhibit proliferation and induce apoptosis in HepG 2 cell line.	(Sanaei et al., 2017)
Dacarbazine and evorolimus	Oleuropein	BRAF mutated melanoma	*In vitro* A375 human melanoma cell line induced with BRAF mutation	Oleuropein successfully increased the cytotoxic effect of Dacarbazine and significantly enhanced Everolimus effects on BRAF melanoma cells, via inhibition of the pAKT/pS6 pathway.	(Ruzzolini et al., 2018)
Cisplatin	Theaflvineflavin-3,3'-digallate (TF3)	Ovarian cancer	*In vitro* A2789, CP70 and OVCAR3 ovarian cancer cell line	TF3 and cisplatin synergistically induced apoptosis and G1/S cell cycle arrest in ovarian cancer cells as well as downregulated Akt phosphorylation in ovarian cancer cells.	(H. Pan et al., 2018)
2-methoxyestradiol (2-ME)	Oleuropein	Osteosarcoma	*In vitro* 143B human osteosarcoma (OS) cell line	Oleuropein significantly enhanced anti-cancer effects of 2-ME on highly metastatic 143B OS cells.	(Przychodzen et al., 2019)
Antimicrobial					
Amphotericin B	Epigallocatechin-3-gallate (EGCG)	Antimycotic-susceptible and -resistant Candida albicans	*In vitro* microbial culture	Combined treatment between EGCG and amphotericin B enhances the antifungal effect of amphotericin B by inhibiting growth of antimycotic-susceptible and -resistant C. albicans by 98.5%–99.7%. as well as allows the use of lower doses of antimycotics.	(Hirasawa & Takada, 2004)
Norfloxacin (NOR), ampicillin (AMP), oxacillin (OXA), ciprofloxacin (CIP)	Curcumin	Methicillin-resistant Staphylococcus aureus (MRSA)	*In vitro* microbial culture	Curcumin in combination with all the four antibiotics effectively inhibit S.aureus growth via reduction in minimal inhibitory concentration (MIC) against MRSA.	(Mun et al., 2013)

Table 1 (cont.): Therapeutic combination of existing therapy with polyphenol on various diseases target.

Drugs or therapeutics approach	Polyphenols	Targets	Experimental models	Experimental findings	Ref
Ciprofloxacin	Phenolic-rich maple syrup extract (PRMSE); active components catechol	Gram-negative clinical strains of Escherichia coli, Proteus mirabilis, and Pseudomonas aeruginosa	*In vitro* microbial culture	PRMSE with ciprofloxacin exhibit synergistic interaction by targeting bacterial biofilm which helps reduced biofilm formation and increased the susceptibility of bacterial biofilms to antibiotics.	(Maisuria et al., 2015)
Fluconazole and amphotericin B	Catechins from Assam and Himachal Pradesh green tea	Candida albicans and candida glabrata	*In vitro* microbial culture and *in vitro* vero cell line	Purified catechins showed synergistic activity with fluconazole and amphotericin B against Candida species with twice MIC compared to any agent alone. Cytotoxicity analysis of the combined treatment depicted high percentage viability from 91.4% to 100% of Vero cell line; suggesting non-cytotoxic activity of proposed composition on healthy cells.	(Anand & Rai, 2017)
Rimfampin (R) and isonic acid (INH)	Polyphenols from Punica stranatum or pomegranate extracts	Multidrug resistance turbeculosis (MDR-TB)	*In vitro* microbial culture	Synergistic effects were observed between R and INH with Punica stranatum extracts against MDR-TB strains. However, combination therapy of R was more effective than INH. Combination of R with Punica stranatum extracts at 15% inhibited 100% (MIC 200%) against MDR-TB strains.	(AlMatar et al., 2019)
Anti-diabetic					
Insulin	Curcumin	Diabetes	*In vitro* C2C12 mouse myoblast cell line	Treatment of insulin and curcumin synergistically and strongly induced glucose uptake and the phosphorylation of AMP-activated protein kinase *in vitro* with increased insulin sensitivity in muscle cells.	(Kang & Kim, 2010)
Oral hypoglycemic drugs (OHD), namely, thiazolidinedione (THZ) and metformin,	Ferulic acid, p-coumaric acid, eugenol, chlorogenic acid, and caffeic acid from dietary polyphenol	Diabetes	*In vitro* 3T3-LI adipocytes cell line	Cinnamic acid, ferulic acid, p-coumaric acid, eugenol, chlorogenic acid, and caffeic acid in combination thiazolidinedione (THZ) and metformin, increases glucose metabolism via increased uptake of 2-deoxyglucose (2DG) by 3T3-L1 adipocytes cells.	(Prabhakar & Doble, 2011)

Table 1 (cont.): Therapeutic combination of existing therapy with polyphenol on various diseases target.

Drugs or therapeutics approach	Polyphenols	Targets	Experimental models	Experimental findings	Ref
Pioglitazone	Ellagic acid	Type II diabetes	*In vivo* diabetes induced rat	Diabetic rats received combination of 10 mg of ellagic acid/kg with 10 mg of pioglitazone/kg showed improvements in all biochemical parameters in comparison to single treatment along with increased the expression levels of GLUT4, PPAR-γ and adiponectin in skeletal muscle.	(Nankar & Doble, 2017)
Cardio-protective effects					
Simvastatin	Chokeberry flavonoid extract (anthocyans, polymeric procyanidines and phenolic acids)	Myocardial infraction (MI)	Clinical trial in patients that survived MI and have received statin therapy at least 6 months	Forty-four patients with mean age 66 years undergone double-blind, placebo-controlled trial. Together with simvastatin, flavonoids from chokeberry extract reduce the severity of inflammation by significantly decreased serum 8-isoprostans and Ox-LDL levels, as well as hsCRP and MCP-1 levels with the reduction in systolic and diastolic blood pressure.	(Naruszewi et al., 2007)
Simvastatin or atorvastatin	Flavonoid-enriched chocolate contained short-term flavan-3-ol and isoflavone	Cardiovascular disease risk	Randomized, double-blind, placebo-controlled clinical trial in postmenopausal women with type II diabetes receiving mg simvastatin or atorvastatin	118 participants aged less or equal to 75 years old undergone the clinical trial. The chocolate enriched flavonoid intervention with existing therapy (simvastatin or atorvastatin) improved pulse pressure variability equated to a 10% cardiovascular disease risk reduction with larger reductions in diastolic blood pressure and mean arterial pressure indicating clinically relevant improvements in arterial stiffness.	(Curtis et al., 2013)
Atorvastatin calcium	Curcumin	Atherosclerosis	*In vitro* human aortic endothelial cells and *in vivo* ApoE knockout (ApoE-/-) mice	Synergistic suppression of adhesion molecules (E-selectin and ICAM-1) and plasma lipid along with secretion of inflammatory factors (IL-6 and MCP-1) on combined atorvastatin calcium and curcumin delivery in vitro. Reduced Ato-inducible cytotoxicity *in vivo* observed in combined treatment. Both *in vitro* and *in vivo* results demonstrated drastically reduces atherosclerotic lesions.	(Li et al., 2019)

Table 1 (cont.): Therapeutic combination of existing therapy with polyphenol on various diseases target.

Drugs or therapeutics approach	Polyphenols	Targets	Experimental models	Experimental findings	Ref
Atorvastatins	Resveratrol	Percutaneous coronary intervention (PCI) for coronary artery disease	*In vivo* rabbits with induced abdominal aorta injury followed by drug - eluting stents (DESs) implantation and *in vitro* bone marrow stem cells (BMSCs)	The area of proliferation and migration of vascular smooth muscle cells in the tunica intima and mean thickness were greater in the combined atorvastatin and resveratrol treatment *in vivo*. Biochemical assays on *in vitro* BMSCs resulted in significantly upregulated Akt, p -Akt, eNOS, p -eNOS , and CXCR4 expression. Both findings exhibited improved re-reendothelialization.	(Chen et al., 2020)
Regenerative effects					
Bone marrow stromal cells (BMSCs)	Green tea polyphenols (GTPs)	Blood-spinal cord barrier (BSCB) after spinal cord injury	*In vivo* rat model with spinal cord injury	Combination of BMSCs and GTPs shown to decrease BSCB permeability that helps to improve spinal cord compression, improve motor function, up-regulated expression of tight junction associated proteins claudin-5, occludin and ZO-1 in rat model with spinal cord injury.	(Yu et al., 2015)
Collagen scaffold	Curcumin based chitosan nanoparticle	Wound healing	*In vivo* rat model	Synergistic combination of Curcumin based chitosan nanoparticle and collagen scaffold indicated faster contracted wound in wound closure analysis and complete epithelialization with thick granulation tissue formation *in vivo*.	(Karri et al., 2016)
Pamidronate	Quercus infectoria extracts	Bone regeneration	*In vitro* hFOB 1.19 human osteoblast cell line	Increased rate of proliferation and significant elevation of Runx2 and Osx expression; biochemical markers for bone tissue regeneration in cells treated with combination of Quercus infectoria extract and pamidronate.	(Raudhah et al., 2018)
Collagen scaffold	P-coumaric acid	Mandible tissue regeneration	*In vivo* rat model with critical size mandible defect.	Impregnation of collagen scaffold loaded with p-coumaric acid and cartilage oligomatrix protein (COMP) enhanced formation of new bone and showed up-regulation of osteogenesis related biochemical markers; Osx, OCN and OPN as well as angiogenesis markers; fibroblast growth factor-2 and VEGF in rat model with critical size mandible defects.	(Bhattarai et al., 2019)

capsulation. The main aims are primarily to increase the efficacy and effectiveness of the readily available therapy; determining the required doses; thus, allowing synergistic interaction.

Mechanism of interaction of combined existing therapy with polyphenols

The capability of polyphenols to regulate the activity of various enzymes and thus to interfere in signaling mechanisms in various cellular processes may be ascribed in part to the physiochemical properties of these compounds that allow them to participate in different metabolic cellular oxidation–reduction reactions. Most documented mechanism of action of polyphenols are via savaging ROS. As mentioned, ROS are produced by human body in a controlled quantity and are capable of unrestricted oxidation of various cellular components that controlled different signal transduction in cells; it can also lead to the oxidative destruction of the cells (Mittler, 2002). Commonly, oxidatively modified forms of proteins accumulate during aging, oxidative stress, and in most pathological conditions of diseases; these had scientist to focused their attention on the modification of biological molecules by various kinds of ROS. Collectively, these ROS can lead to oxidation of amino acid residue side chains, formation of protein-protein cross-linkages, and oxidation of the protein backbone and deoxyribonucleic acid (DNA) modification that may help in development of targeted therapy for management of various disease (Balaban et al., 2005; Buttke & Sandstrom, 1994; Finkel & Holbrook, 2000).

As previously mentioned, development of newly discovered drugs or synthetic compounds could take up to years involving tremendous experimental research and multiple clinal trial in order for it to be marketable and confirmed the safety of its use (Barden & Weaver, 2010). Hence, taking into consideration the immense benefits offered by polyphenolic compounds; as listed in table 1; this review uncovers successful studies on the combination of polyphenols with readily available drugs or therapeutic approaches targeted on various diseases and its ability to increase drugs along with therapeutic efficacy. As a consequence, may fast tract the process of new drug-natural product discovery.

Combination of chemotherapeutic agents with polyphenols

Despite many advances in the treatment for most forms of cancer, the mortality and relapse rate remain high. Since there is no definitive treatment for cancer, many efforts have been made in order to find a breakthrough in cancer. We have compiled a list of successful combination treatment in cancer therapy employing the use of standard chemotherapeutics drugs with polyphenols targeted for different types of cancer. An ideal treatment combination should achieve synergistic effects via measurement of various biochemical markers. Studied on the successful *in vitro* assessment of combined treatments between chemotherapeutics agents and polyphenols on targeted cancer cell lines exhibited improved or increased inhibition of cancer cells via direct anti-proliferative and pro-apoptotic effects (Alshatwi et al., 2016; Cromie & Gao, 2015; Gheybi et al., 2019; Liang et al., 2010; Mahbub et al., 2015; Menendez et al., 2007; Nihal et al., 2010; Przychodzen et al., 2019; Ruzzolini et al., 2018; Sanaei et al., 2017; Sartippour et al., 2006; Singh et al., 2015). Additionally, some of the studies has shown that the presence of polyphenols increased the efficacy of chemotherapeutic agents used against the studied cancer cell line compared to any of the agents alone (Cromie & Gao, 2015; Liang et al., 2010; Mahbub et al., 2015; Menendez et al., 2007; Ruzzolini et al., 2018; Sartippour et al., 2006). The biological activity of combined treatment between chemotherapeutic drugs and polyphenols has been extensively studied in the preclinical assays. Some combined treatments are more effective in overcoming cancer chemotherapeutic resistance by modulating cancer cells with multiple drug resistance (MDR) overexpression phenotype (Liang et al., 2010; Sartippour et al., 2006). A part from that, some of the studies has shown that synergy combination between chemotherapeutic drugs and polyphenols, exert an important role in apoptosis induction, cell cycle arrest and oxidative stress *in vitro* (Alshatwi et al., 2016; Kiemlian Kwee, 2016; Pan et al., 2018). Moreover, *in vivo* study demonstrated suppression of angiogenesis is translated to larger areas of necrosis and lower blood vessel density in the treated xenografts (Sartippour et al., 2006). *In vivo* experimental results also showed promising potential of long-term tumor free survival in the experimental model (Du et al., 2010; Singh et al., 2015). Regardless of the successful preclinical findings documented, clinical trial has yet to be truly investigated for combined treatment between chemotherapeutic drugs and polyphenols. Bayet-Robert et al, however; demonstrated significant improvement in clinical presentation and biological response in a phase I clinical trial conducted among advanced metastatic breast cancer patients receiving doxetacel (chemotherapeutics drugs) and curcumin (polyphenols) (Bayet-Robert et al., 2010). Hence, this has shown the significant possibility of successful clinical trial of the combined treatment.

Combination of antimicrobial drugs with polyphenols

Antimicrobial drugs act by interfering with the life cycle of an organism in various ways by binding to a cellular target that results in the alteration of the normal function of the microorganism, leading to either inhibition of growth or cell death. A part from that, in order for the antimicrobial agent to reach its target site, the drug must also possess sufficient affinity for its receptor (Neely &

Jelliffe, 2017). These pharmacological characteristics are the primary determinants of antimicrobial activity. Some of these drugs is notorious for developing rapid resistance to antibiotics, caused primarily by antibiotic selection and the horizontal transfer of resistance genes. Based on the previous findings, it has been reported that polyphenols also serve a beneficial role as potent antimicrobial agents. Therefore, this study was investigated to assess whether polyphenols in combination with antibiotics has the potential qualities of alternative therapeutic agents to overcome the antibiotic resistance of various microbial strains. Studies from various documented literature has shown synergistic interaction between combination treatment of antimicrobial drugs and polyphenols causing increased in drug's efficacy against various MDR strains includes *candida albicans* (Anand & Rai, 2017; Hirasawa & Takada, 2004), MRSA (Mun et al., 2013) and MDR-TB (AlMatar et al., 2019) in *in vitro* microbial culture. Moreover, research by Maisuria *et al*, indicated the successful combined treatment between PRMSE and ciprofloxacin on targeting bacterial biofilm and reducing its formation in clinical strains of *Escherichia coli, Proteus mirabilis*, and *Pseudomonas aeruginosa* (Maisuria et al., 2015). Based on the successful synergistic combination recorded, there's the need for further *in vivo* testing for development of an efficient and safer combinational drug against various microbial agent.

Combination of antidiabetic agents with polyphenols

Diabetes is a group of heterogeneous disorders that are commonly presented with hyperglycemia and glucose intolerance, due to insulin deficiency, impaired insulin action or sometimes could be both. According to the World Health Organization (WHO), diabetes mellitus (DM) is the most common endocrine disorder that are now affecting at least 171 million people worldwide (Wild et al., 2004). Hence, there is a necessity for new antidiabetic agents with a better therapeutic efficacy and less adverse effects. Previous study has demonstrated significant roles of polyphenols in glucose metabolism through scavenging of free radicals, and its role on oxidative stress-linked cell signaling which are the key towards uncovering the therapeutic intervention of DM (Kamalakkannan & Prince, 2006; Veerapur et al., 2017). Hence, in this literature, we present the successful increase in efficacy of antidiabetic drugs when combined together with polyphenols *in vitro* (Kang & Kim, 2010; Prabhakar & Doble, 2009; Prabhakar et al., 2011) and *in vivo* (Nankar & Doble, 2017) experimental model. The ability of polyphenols; curcumin as a potent antioxidant in glucose metabolism was shown through AMPK/ACC pathway activation that results in enhanced insulin sensitivity *in vitro* (Kang & Kim, 2010). Meanwhile, dietary polyphenols from cinnamic acid, ferulic acid, p-coumaric acid, eugenol, chlorogenic acid, and caffeic acid in combination thiazolidinedione (THZ) and metformin also demonstrated to help increases glucose metabolism (Prabhakar & Doble, 2011). The dietary intake from plant source and their ingredients could be a more effective strategy for the management of DM because of the likelihood of high compliance not to mention; these dietary polyphenols are free from side effects, have better effectiveness, act on multiple target sites, and relatively cost effective. Hence, these studies has shown the potential reduced therapeutic concentration of anti-diabetic drugs when combined with polyphenols, that in returns will cause the side effects to be decreased to a large extent (Prabhakar & Doble, 2009) In addition, understanding the metabolism and bioavailability of the interaction between these two compounds are vital. A part from that, these findings support a potential clinical application of combination treatment between polyphenols and antidiabetic agents in measurement of DM and its complications.

Cardioprotective effects in combined polyphenols treatment with synthetic drugs

The antioxidant properties of many polyphenols alone could have been proclaim to exhibit vasodilator, antithrombotic, anti-inflammatory, antiapoptotic, hypolipemic or antiatherogenic effects (Williams et al., 2004) that have been associated with decreased cardiovascular risk. Studies have shown that polyphenols contribute to vasodilator effects and can help to improve lipid profiles as well as mediates the oxidation of low-density lipoproteins. In addition, these polyphenols can also attenuate apoptotic process in vascular endothelium and contributes to anti-inflammatory effects. Hence, polyphenols can be considered good candidates for the prevention and treatment of cardiovascular diseases (Quinones, et al., 2013). Based on table 1, combination treatment between selected cardiovascular drug and polyphenols causes reduced atherosclerosis lesion and improved vascular re-reendothelialization *in vivo* (Chen et al., 2020; Li et al., 2019). These findings were supported by successful clinical trial incorporating combined polyphenols intake with cardiovascular drug therapy. Results of the clinical trial indicated that the action of combined compounds causes decrease of endothelial inflammation and mediation of vascular wall repair (Naruszewicz et al., 2007) Moreover, it was uncovered that the combination treatment also causes significant clinical improvement that includes decreased in pulse pressure variability, diastolic blood pressure and mean arterial pressure indicating relevant improvements in arterial stiffness (Curtis et al., 2013). Generally, the evidence listed provide researchers and clinicians with an outline to consider these combined approached as a readily available solution to helps reduced cardiovascular disease risk among high-risk patients.

Regenerative effects of combined therapeutic approaches and synthetic drugs with polyphenols

Regenerative medicine has been extensively explored to as an ideal solution for numerous existing diseases. The key factor in regenerative medicine is to replace or "regenerating" human cells, tissues or organs to restore or establish normal human function. The use of natural product and drug either by itself of synergistically combined, has been published in many researches as a drive component in regenerative medicine (Douglas et al., 2018). Current approaches in regenerative medicine is either via targeted drugs, cellular material, biomaterials as well as other therapeutic approaches that aims to mediate cellular regeneration and growth. Hence, in this review, the potential used of polyphenols combined with some of readily applied therapeutic approaches or drugs on cell regeneration to promotes healing were demonstrated. Yu *et al*, demonstrated the successful combination between bone marrow stromal cells (BMSCs), and green tea polyphenols on improving the condition of spinal cord injury in a rat model *in vivo* (Yu et al., 2015). Moreover, Raudhah *et al*, indicated successful combination between osteoporotic drug and polyphenols in bone regeneration *in vitro* (Raudhah et al., 2018). Additionally, the incorporation of material such as collagen scaffold combined with polyphenols was found to be successful for improving wound healing (Karri et al., 2016) and bone regeneration (Bhattarai et al., 2019) *in vivo*. Thus, these findings indicated various potential that can be explored to mitigate readily available drugs, biomaterial and synthetic material in order to promotes cell regeneration.

Conclusion

In summary, synergistic effects are achieved when two compounds increase each other's effectiveness by more than the sum of their single agent responses. We conclude that the use of polyphenols in combination of synthetic drugs or other therapeutic approaches against various diseases has significant preclinical effects; however, the evidence on clinical trial is still lacking and need to be uncover. The advantage of designing treatment regimens of synergistic combination in a particular disease setting provide the opportunity to lower the dosage of an individual agent, thereby reducing toxicity while maintaining the wanted effect on the target cells (Jia et al., 2009). Additionally, synergistic combination on the use of biomaterials was shown to enhanced its acceptance. Thus, provided numerous successful researches reported in this literature; it is strongly recommended that prioritizing the pharmacodynamics and pharmacokinetics concept in designing treatment combination should be considered in the later stages of clinical testing for optimization of successful clinically utilizable therapies.

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Availability of data and materials

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Authors' contribution

ARA, HH and NMZ drafted the manuscript. All authors read and approved the final manuscript. First author information ARA (Ph.D) is a lecturer in the Department of Biomedical Science 1, Faculty of Medicine and Health Science, Universiti Sains Islam Malaysia.

Conflict of Interest

The authors declare that they have no competing interests.

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