REVIEW ARTICLE

Resveratrol and its biological actions

Praharsh K. Shah, Jagruti A. Patel
Department of Pharmacology, Institute of Pharmacy, Nirma University of Science and Technology, Sarkhej-Gandhinagar Highway, Ahmedabad-382 481, India

Resveratrol is a phytoalexin that is found in a few edible food materials such as grape skins, pea-nuts and red wine. Numerous reports exists in the literature suggesting that dietary resveratrol may act as an antioxidant, promotes nitric oxide production, inhibits platelet aggregation and increases high-density lipoprotein cholesterol, and subsequently may serve as a cardio-protective agent. Recent reports demonstrated that resveratrol can function as a cancer chemopreventive agent, exhibiting anti-inflammatory, neuroprotective, anti-ageing and antiviral properties. However, most of these effects are yet to be confirmed in humans. In the only clinical trial, high doses of special proprietary formulation has demonstrated blood sugar-lowering effects of resveratrol in type 2 diabetes mellitus. As with many polyphenols, resveratrol is reasonably well absorbed but has low bioavailability. It is metabolized by hydroxylation, glucuronidation, sulfation and hydrogenation. We reviewed the published literature and reports to consolidate information available on the biological activity of resveratrol using electronic databases as well as handpicked articles to summarize the biological effects of resveratrol and its clinical benefits against human diseases.

Key words: Resveratrol, chemoprevention, cardio-protection, anti-inflammatory effects

INTRODUCTION

Resveratrol (3,5,4′-trihydroxy-trans-stilbene) is a phytoalexin that is produced naturally by several plants such as eucalyptus, spruce, Vitis vinifera, labrusca and muscadine grapes and by other foods such as mulberries and peanuts.[1] It is produced in the plant by the action of either a fungus, stress, injury, infection or ultraviolet irradiation. Resveratrol was originally isolated from the roots of white hellebore in 1940, and in 1963 from the roots of Japanese knotweed. However, it attracted a wider attention only in 1992, when the cardio-protective effect of red wine was attributed to the presence of resveratrol.[2] In traditional Indian system of medicine, its use dates back some 1000 years, where resveratrol is described as the main ingredient of Darakchasava—an ayurvedic medicine prescribed as a cardiotonic in India.[3] In grapes, resveratrol is found primarily in its skin and also in red wine. The amount found in grape skin also varies with the grape cultivar, its geographic origin and exposure to fungal infection. The amount of fermentation time a wine spends in contact with grape skin is an important determinant of its resveratrol content.[4]

Resveratrol is a stilbenoid, a derivative of stilbene, derived from the enzyme stilbene synthase using one molecule of 4-coumaroyl-Co-A and three molecules of malonyl-CoA as substrates. It exists as two geometric isomers: *Cis*- [*Z*] and *trans*- [*E*]. *Trans*-resveratrol in the powder form is stable under 'accelerated stability' conditions of 75% humidity and 40°C in the presence of air. Resveratrol content also remains stable in the skin of grapes and pomace taken after fermentation and when stored for a longer periods of time.[5]

Reports in the literature exist suggesting that dietary resveratrol may act as an antioxidant,[6-9] promote nitric oxide (NO) production,[10,11] inhibit platelet aggregation,[2,12,13] increase high-density lipoprotein cholesterol[14] and hence also act as a cardio-protective agent.[15] It has also been proposed that resveratrol has anti-inflammatory,[16] neuroprotective, antiviral activities[17,18] as well as it can function as a cancer chemopreventive agent.[19-22] In the present review, an attempt has been made to summarize various biological aspects of resveratrol and emphasis has been made to focus its potential health benefits for the betterment of mankind.

MATERIALS AND METHODS

A literature survey was carried out to assess the published literature for the appraisal of information available on the biological effects of resveratrol. As per the guidelines for the use of electronic and internet media,[23-26] a high quality and reliable medical information from the Internet was retrieved only from the Health On Net (HON) conduct certified and accredited websites like Entrez PubMed (Medline), CAM-PubMed, Allied and Complementary Medicine Database, Natural Medicine Comprehensive

Address for correspondence: Dr. Jagruti A. Patel, Associate Professor and Head, Department of Pharmacology, Institute of Pharmacy, Nirma University of Science and Technology, Sarkhej-Gandhinagar Highway, Ahmedabad-382 481, India. E-mail: jagrutiap@gmail.com
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Database and Embase and Cochrane library. The databases were searched using the search terms 'resveratrol, chemo-prevention, cardio-protection, anti-inflammatory actions, biological actions, bioavailability and metabolism, clinical trials' etc. Non-English language citations were excluded. The bibliographies of the retrieved articles were checked for any additional pertinent studies. An extensive review of literature identified that published articles were mainly based on pre-clinical studies, *in vitro* studies and limited clinical observations. The nature of findings and published observations were then abstracted and compiled in the present review.

Effects of Resveratrol on Cancer

Resveratrol blocks the multistep process of carcinogenesis, tumour initiation, promotion, and progression, and suppresses the angiogenesis and metastasis.[21,27] As an anticancer agent, it has primarily been linked to growth and death regulatory pathways. There is now growing evidence that, under physiological conditions, it contributes to the maintenance of genome stability. Thus, at the stage of DNA damage formation, it protects the genome as an antioxidant via inhibition of inflammation, suppression of metabolic carcinogen activation, *de novo* expression of genes that encode detoxifying proteins and possibly even via radical scavenging properties.[28,30]

It induces apoptosis by up-regulating the expression of Bax, Bak, PUMA, Noxa, Bim, p53, TRAIL, TRAIL-R1/DR4 and TRAIL-R2/DR5 and simultaneously by down-regulating the expression of Bcl-2, Bcl-XL, Mcl-1 and surviving.[29] Resveratrol causes growth arrest at G1 and G1/S phases of the cell cycle by inducing the expression of CDK inhibitors $p21^{/WAF1/CIP1}$ and $p27^{/KIP1}$; a cancer chemopreventive agent, resveratrol has been shown to inhibit tumour initiation, promotion and progression of a wide variety of tumour cells, including lymphoid and myeloid cancers; multiple myeloma; cancers of the breast, prostate, stomach, colon, pancreas, and thyroid, melanoma; head and neck squamous cell carcinoma; ovarian carcinoma and cervical carcinoma.[4,22,31-33] Besides chemopreventive affects, resveratrol appears to exhibit therapeutic effects against cancer also [Figure 1].[34]

However, resveratrol undergoes avid metabolism in humans, which limits the availability of the parent molecule at organs remote from the site of absorption targeted for chemoprevention.[35] It remains to be determined if repeated dosing schedules can achieve higher systemic concentrations of resveratrol than those observed after a single dose, or whether sulfate and glucuronide metabolites, which are generated abundantly in the human biophase after resveratrol ingestion, possess efficacy in and of themselves.

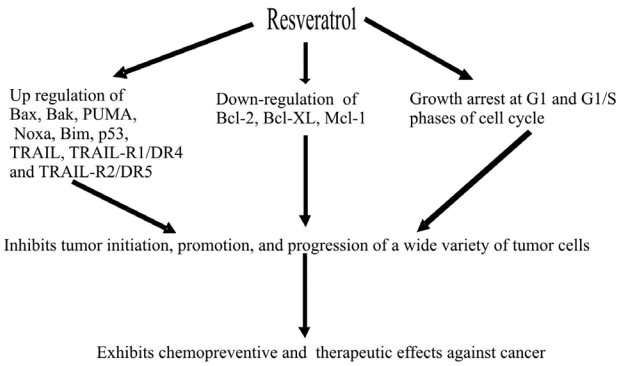

Figure 1: Schematic representation of the mechanism of resveratrol as an anti-cancer agent

Effects of Resveratrol on Cardio-Vascular Disease

Several reports suggest that at low doses (such as consumed in common diet), resveratrol may have cardio-protective activity.[2,6-15] It demonstrates both negative chronotropic and negative inotropic action, which may be attributed to its ability to open K [ATP] and Kc [Ca] channels.[36] The cardio-protective ability of resveratrol may also result from its anti-inflammatory functions in the ischaemic heart.[37] Treatment with resveratrol significantly improved post-ischemic ventricular function and reduced myocardial infarct size compared to the non-treated control group.[6] The amount of pro-adhesive molecules, including soluble intracellular adhesion molecule-1 (sICAM-1), endothelial leukocyte adhesion molecule-1 (sE-selectin) and vascular cell adhesion molecule-1 (sVCAM-1) were each significantly decreased during reperfusion in the resveratrol-treated group. Nitro-L-arginine methyl ester (L–NAME), an NO blocker, completely abolished these beneficial effects of resveratrol. The results support an anti-inflammatory action of resveratrol through a NO-dependent mechanism to be the basis of its cardio-protective action.[10,11]

Resveratrol protects the heart against ROS-mediated menadione (i.e., vitamin K_3) toxicity by inducing NAD[P] H: Quinone oxidoreductase, also known as DT-diaphorase, a detoxifying enzyme for quinone-containing substances.[38] The cardio-protective effect of resveratrol was also attributed to its ability to up-regulate catalase activity in the myocardium. Resveratrol functions as *in vivo* antioxidant and can scavenge peroxyl radicals in the heart.[6,8] A commercial preparation of resveratrol made from *Polygonum cuspidatum* root extract [Protykin®] also scavenges peroxyl radicals and protects the heart from ischaemia reperfusion injury.[6,16,39]

Resveratrol appears to induce an anti-apoptotic signal for the protection of the heart. In porcine coronary arteries, short-term treatment with resveratrol significantly inhibited mitogen-activated protein kinase (MAPK) activities, and

immuno-blot analyses revealed consistent reduction in the phosphorylation of extracellular signal-regulated kinases 1/2 (ERK1/2), Jun N-terminal kinase (JNK-1), and p38 MAPK.[40] The same study found that resveratrol attenuated basal and endothelin-1 (ET-1)-mediated protein tyrosine phosphorylation. Anti-apoptotic function of resveratrol is further supported by several other studies, which have demonstrated a reduction of apoptotic cardiomyocytes in the ischaemic reperfused heart that had been pre-treated with resveratrol.[41]

A study from France reported that daily consumption of red wine prevents atherosclerosis not through its action on HDL-cholesterol, but due to its ability to inhibit platelet aggregation [Figure 2].[11,38]

Thus, results of various studies suggest that resveratrol modulates vascular cell function, inhibits LDL oxidation, suppresses platelet aggregation, produces anti-apoptotic effects and reduces myocardial damage during ischaemia reperfusion.[6] These studies indicate that resveratrol may emerge as a promising cardiovascular protective agent. However, more studies are needed to establish its bioavailability and *in vivo* cardio-protective effects in humans.

Antiviral Effects of Resveratrol

Resveratrol seems to increase the potency of some antiretroviral drugs against HIV *in vitro*. Infection by herpes simplex virus ordinarily activates the cell protein nuclear factor κB (NF-κB). A study undertaken on *in vitro* cells found that resveratrol suppresses the activation of this transcription- and apoptosis-related protein. The study further found that multiple viral protein products were either reduced or completely blocked along with a marked reduction in the viral DNA production.[17] Another cell culture study demonstrated that resveratrol blocked the influenza virus from transporting viral proteins to the viral assembly site, hence restricting its ability to replicate.[18]

Effects of Resveratrol on Inflammation

The anti-inflammatory role of resveratrol was evident from a study where resveratrol effectively suppressed the aberrant expression of tissue factors (TF) and cytokines in vascular cells. Resveratrol, in a dose-dependent manner, inhibited the expression of TF in endothelial cells stimulated with a variety of agonists, including interleukin-1ß (IL-1ß), tumour necrosis factor-α (TNF-α) and lipopolysaccharide (LPS). Resveratrol has also been shown to reduce inflammation via inhibition of prostaglandin production, cyclo-oxygenase-2 (COX-2) activity and NF-κB activity.[42]

Several studies have reported that resveratrol potentiates down-regulation of inflammatory response, probably by inhibition of synthesis and release of pro-inflammatory

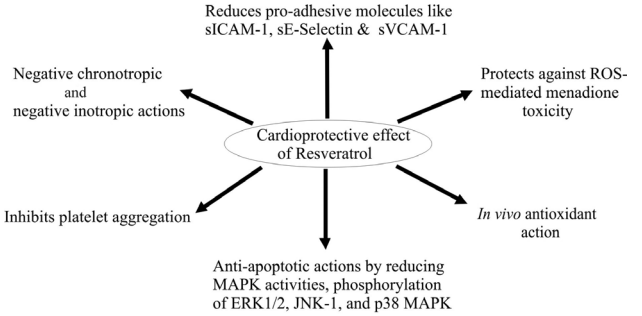

Figure 2: Schematic representation of resveratrol as a cardioprotective agent

mediators, modification of eicosanoid synthesis, inhibition of activated immune cells, or by inhibiting inducible NO synthase (iNOS) and COX-2 activity via its inhibitory effects on NF-κB or the activator protein-1 (AP-1).[1,16]

Resveratrol when administered to cases of trauma-hemorrhage reduced hepatic injury by reduction of pro-inflammatory mediators via an Estrogen Receptor-related pathway. It suppressed the activity of T and B cells and macrophages by significant inhibition in proliferation, antibody production and lymphokine secretion.[43]

Antioxidant Effects of Resveratrol

Resveratrol is an effective scavenger of hydroxyl, superoxide, metal/enzymatic-induced and cellular-generated radicals.[6-9] Resveratrol can maintain the concentrations of intracellular antioxidants found in biological systems. For example, resveratrol maintained glutathione (GSH) amounts in oxidation-stressed peripheral blood mononuclear cells isolated from healthy humans. Similarly, resveratrol restored glutathione reductase in cells subjected to TPA-mediated oxidative stress. In human lymphocytes, resveratrol increased the amounts of several antioxidant enzymes, including glutathione peroxidase, glutathione-*S*-transferase and glutathione reductase.[44]

Resveratrol is also capable of scavenging some intracellular reactive oxygen species (ROS). A recent review reported that a skin care formulation with resveratrol demonstrated nearly 17 times greater antioxidant activity than idebenone.[45] Resveratrol may act as a neuroprotective agent for the treatment of neuro-degenerative conditions.[46,47] Alzheimer's disease exhibits elevated levels of malondialdehyde (MDA) and nitrites, with a concurrent depletion in GSH transferase and acetyl cholinesterase activity. Pretreatment with resveratrol replaces the normal concentration of MDA and nitrites etc., thus demonstrating its beneficial effects.

Effect of Resveratrol on Nitric Oxide Production

A direct role for NO in vasorelaxation was identified when increased NOS activity was found in cultured pulmonary artery endothelial cells treated with resveratrol,

suggesting that resveratrol could afford cardio-protection by affecting the expression of NOS.[48] The extracts of wine or grape increased guanosine 3',5'–monophosphate (cGMP) amounts in intact vascular tissue and both relaxation and the increase in cGMP were reversed by N^G-monomethyl-L-arginine or by N^G-nitro L-arginine-competitive inhibitors of the synthesis of the endothelium-derived relaxing factor, NO, suggesting that vasorelaxation induced by grape products is mediated by the NO–cGMP pathway.[49]

Consistent with these results, resveratrol protected perfused working rat hearts through increased iNOS expression. The cardio-protective ability of resveratrol was abolished with an iNOS inhibitor, aminoguanidine. Resveratrol also failed to provide cardio-protection in iNOS knockout mice.[50] In a recent study, however, resveratrol reduced myocardial ischaemia reperfusion injury through both iNOS-dependent and iNOS-independent mechanisms by increasing the expression of iNOS, endothelial NOS (eNOS) and neuronal NOS (nNOS).[11]

Effects of Resveratrol on Platelet Aggregation

Resveratrol inhibits platelet aggregation induced by collagen, thrombin or ADP.[2,12,13] It also interfered with the release of inflammatory mediators by activated polymorphonuclear cells (PMN) and decreased the adhesion-dependent thrombogenic functions of PMN.[44] *Trans*-resveratrol inhibited, in a dose-dependent manner, the arachidonate-dependent synthesis of the inflammatory agents like thromboxane B2 (TxB2), hydroxyheptadecatrienoate (HHT) and 12-hydroxyeicosatetraenoate (12-HETE).[51]

It was found that resveratrol blocked platelet aggregation and platelet P-selectin expression. Resveratrol could reduce the ratio of phospho-phospholipase C beta 3 (P-PLC beta 3) and total-phospholipase C beta 3 (T-PLC beta 3), which play key roles in the signal transduction system of platelets in human. So resveratrol suppresses platelet aggregation and P-selectin expression partly through the decrease of the activity of phospholipase C beta of platelets.[52]

Other Actions of Resveratrol

Resveratrol extended the lifespan of several short-living species of animals; however, this effect has not been demonstrated in mammals. In 2003, Howitz and Sinclair reported that resveratrol significantly extended the lifespan of the yeast *Saccharomyces cerevisiae*.[53] Later on, there were reports that resveratrol also prolonged the lifespan of the worm *Caenorhabditis elegans* and the fruit fly *Drosophila melanogaster*.[54] However, controversy emerged in 2007, as Gruber *et al*.[55] reproduced the above results on *C. elegans*, whereas no consistent increase in the lifespan of either *Drosophila* or *C. elegans* was observed by Bass and co-workers.[56] Meanwhile in 2006, a median life span extension of 56% was observed in a short-lived vertebrate fish, *Nothobranchius furzeri* following administration of resveratrol.[57] Besides lifespan extension, resveratrol administration showed significantly higher general swimming activity and better learning ability to avoid an unpleasant stimulus. Further, Baur *et al*.[58] reported that the detrimental effects of high fat diet in mice was counteracted by administration of resveratrol. Both the groups of mice, one receiving the standard diet and another fed with high fat diet plus 22 mg/kg resveratrol demonstrated a 30% lower risk of death when compared to mice on high fat diet. Resveratrol significantly inhibited the high fat diet-induced alteration in gene pathways. Further, resveratrol administration to high fat diet-administered mice was able to counteract the increase in insulin and glucose levels, whereas their free fatty acids and cholesterol levels were much higher when compared to mice on standard diet. Thus, the molecular mechanisms of resveratrol as an anti-ageing agent are not fully understood. However, activation of Sirtuin deacetylases and PGC-1α (peroxisome proliferator-activated receptor co-activator-1 alpha) is believed to be involved in the caloric restriction-longevity effects of resveratrol.[59]

Caloric restriction has been proven to extend the lifespan of a number of species, including mammals by targeting various enzymes, e.g. Sir2. In yeast, a caloric restriction stimulates the activity of an enzyme referred to as Sir2. Administering resveratrol to yeast increased Sir2 activity in the absence of caloric restriction and extended the replicative lifespan of yeast by 70%. Thus, recent data provide interesting insights into the effect of this agent on the lifespan of yeast, flies and fish implicating the potential of resveratrol as an anti-aging agent in treating age-related human diseases.[53,54,56,57]

Resveratrol demonstrates a direct insulin-suppressive action in rats.[59] and may be beneficial in treating diabetic neuropathic pain. Diabetic neuropathic pain is one of the most important microvascular complications associated with diabetes mellitus. Insulin when combined with resveratrol and curcumin was found to inhibit TNF-α and NO levels, indicating its antinociceptive activity. Hence, resveratrol may be used in the treatment of diabetic neuropathic pain.[60]

It has been found that the effects of resveratrol are indeed due to the activation of *SIRT1*. In a study on 123 Finnish adults, those born with certain increased variations in the *SIRT*1 gene, had faster metabolisms, helping them to burn energy more efficiently, indicating that resveratrol may be effective in improving the athlete's performance.[61]

Resveratrol increases blood testosterone concentrations, testicular sperm counts and epididymal sperm motility

and causes penile erection, without any influence on sperm deformity.[62] Again, there is no published evidence anywhere in the scientific literature of any clinical trial for efficacy in humans. There are limited human safety data. It is premature to take resveratrol and expect any particular results. Long-term safety has not been evaluated in humans.

Bioavailability and Metabolism of Resveratrol

In a study conducted by Urpi Sarda *et al*.,[63] the hypothesis was tested that in healthy humans, per oral administration of resveratrol is safe and results in measurable plasma levels of resveratrol. A phase I study of oral resveratrol (single doses of 0.5, 1, 2.5 or 5 g) was conducted in 10 healthy volunteers per dose level. Resveratrol and its metabolites were identified in plasma and urine by high-performance liquid chromatography-tandem mass spectrometry and quantitated by high-performance liquid chromatography-UV. Consumption of resveratrol did not cause serious adverse events. Resveratrol and six metabolites were recovered from plasma and urine. Peak plasma levels of resveratrol at the highest dose were 539±384 ng/mL (2.4 μmol/L, mean±SD; n=10), which occurred 1.5 hours post-dose. Peak levels of two monoglucuronides and resveratrol-3-sulfate were 3- to 8-fold higher. The area under the plasma concentration curve (AUC) values for resveratrol-3-sulfate and resveratrol monoglucuronides were upto 23 times greater than those of resveratrol. Urinary excretion of resveratrol and its metabolites was rapid, with 77% of all urinary agent-derived species excreted within 4 hours after the lowest dose. Excretion was mainly through urine (~73%) and faeces after 12 hours.[64] After oral dose (25 mg) of ^{14}C-labelled resveratrol in humans, it has been confirmed that resveratrol undergoes enterohepatic recirculation. Half life of resveratrol and its metabolites was 9 hours.[35] The low bioavailability of resveratrol across mice, rats and humans has been reported previously also.[35,65,66]

Resveratrol is metabolized by hydroxylation, glucuronidation, sulfation and hydrogenation. In humans[35,65] and rats,[66] resveratrol rapidly undergoes conjugation resulting in <5% of the oral dose being observed as free resveratrol in blood plasma. Few authors, however, have studied resveratrol metabolism in humans. As with many polyphenols, resveratrol is reasonably well absorbed but has low bioavailability.[65] Therefore, the health benefits attributed to the ingestion of resveratrol may most likely be related to its biologically active metabolites. *In vivo* characterization of resveratrol's metabolic profile may reveal which metabolites act as signalling molecules within tissues or reach target organs and account for the health benefits of resveratrol.[31]

Adverse Effects of Resveratrol

A study found that a single dose of upto 5 g of *trans*-resveratrol caused no serious adverse effects in human volunteers.[35] Resveratrol may stimulate the growth of human breast cancer cells, possibly because of its chemical structure, which is similar to a phytooestrogen.[67,68] However, several studies have reported that resveratrol actually fights breast cancer.[27,28]

As resveratrol is oestrogenic, it may interfere with oral contraceptives and hence is contraindicated in pregnant women. No data regarding effects of resveratrol on natural development of children or young adults <18 are available, hence should be contraindicated for use in youngsters and teenagers, until further reports are available.

Clinical trials of resveratrol

Sirtris Pharmaceuticals, Inc., USA has developed a Proprietary Formulation [SRT501] of resveratrol for the treatment of type 2 diabetes. The phase 1 clinical trial, which tested either 1.25 or 2.5 g of SRT501 given twice daily to type 2 diabetic patients, found that the patient group receiving 2.5 g twice a day had significantly lower blood glucose levels as determined through an oral glucose tolerance test (OGTT) during the test at 2-hour time point, as compared with the placebo group.[69]

Thus, there is growing evidence that resveratrol can prevent or delay the onset of various human disorders like cancers, heart diseases, ischaemic and chemically induced injuries, pathological inflammation and viral infection [Figure 3]. Lot of interest in this compound has been renewed in recent years, right from its identification as a chemopreventive agent for a variety of cancers, to subsequent reports that it has cardio-protective effects, also that it extends the lifespan of lower organisms, to its recent clinical trials for type 2 diabetes mellitus. Despite scepticism concerning its bioavailability, an ever-increasing body of evidence, in the form of scientific reports pouring in from various laboratories all over the world, indicate the merits and therapeutic potential of resveratrol against a variety of human disorders.

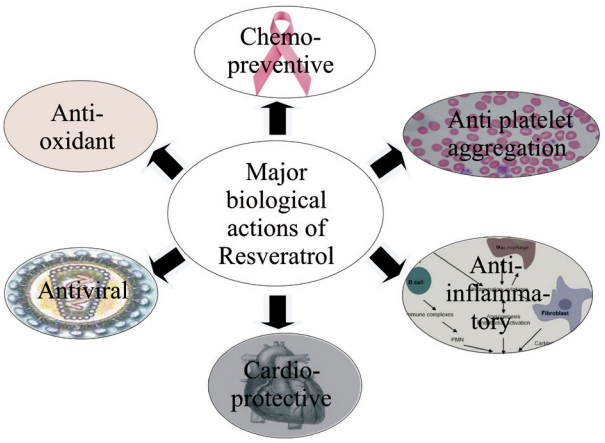

Figure 3: Summary of major biological actions of resveratrol

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