Effects of the Gut microbiota on Amygdalin and its use as an anti-cancer therapy: Substantial review on the key components involved in altering dose efficacy and toxicity

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A B S T R A C T
Conventional and Alternative Medicine (CAM) is popularly used due to side-effects and failure of approved methods, for diseases like Epilepsy and Cancer. Amygdalin, a cyanogenic diglycoside is commonly administered for cancer with other CAM therapies like vitamins and seeds of fruits like apricots and bitter almonds, due to its ability to hydrolyse to hydrogen cyanide (HCN), benzaldehyde and glucose. Over the years, several cases of cyanide toxicity on ingestion have been documented. In-vitro and in-vivo studies using various doses and modes of administration, like IV administration studies that showed no HCN formation, point to the role played by the gut microbiota for the commonly seen poisoning on consumption. The anaerobic Bacteriodetes phylum found in the gut has a high β-glucosidase activity needed for amygdalin hydrolysis to HCN. However, there are certain conditions under which these HCN levels rise to cause toxicity. Case studies have shown toxicity on ingestion of variable doses of amygdalin and no HCN side-effects on consumption of high doses. This review shows how factors like probiotic and prebiotic consumption, other CAM therapies, obesity, diet, age and the like, that alter gut consortium, are responsible for the varying conditions under which toxicity occurs and can be further studied to set-up conditions for safe oral doses. It also indicates ways to delay or quickly treat cyanide toxicity due to oral administration and, reviews conflicts on amygdalin’s anti-cancer abilities, dose levels, mode of administration and pharmacokinetics that have hindered its official acceptance at a therapeutic level.

1. Introduction
Combined surgery, radiation therapy and chemotherapy are the commonly used cancer treatments that people turn to, when diagnosed with cancer. These treatments give a better prognosis but, cases of toxicity and failure of such methods are not uncommon [1]. In such cases, people tend to turn to alternative treatments, also known as CAM (conventional and alternative medicine), claimed to be fruitful as a single or combined treatment [2,3]. Amygdalin is naturally occurring cyanogenic glycoside compound present in fruits and seeds of fruits like apricot, peaches and bitter almonds and it was falsely considered as a vitamin and was used for cancer treatment in late 1950s. Eating amygdalin will cause cyanide poison as amygdalin molecule has nitrile group and could be released as cyanide anion due to the action of beta-glucosidase in human body. Laetrile is a man made synthetic compound from natural amygdalin and was also used for anticancer treatment during 1970s [2].

When NCI carried out 22 case studies pertaining to the use of Laetrile as an alternative therapy, 6 successful cases were found and the FDA banned the use of Laetrile in 1979 [2,4]. Several cases of toxicity have been reported due to the consumption of amygdalin which caused cyanide toxicity (Table 1). An instance of hydrogen cyanide toxicity in animals was first reported in cattle due to consumption of Holocalyx Glaziovii leaves (found in Brazil, Argentina and Paraguay) due to prunasin, another cyanoglycoside, and was later confirmed by Silvana et al. in Wistar rats [5].

Various animal studies and cases of human consumption point out the danger of oral administration of amygdalin [5,6]. Table 8 shows how the activity of intestinal microflora upon these cyanoglycosides has been proved to lead to the formation of hydrogen cyanide (HCN) [2,7]. One of the first studies to prove this employed cyasin, a cyanogenic glycoside. It was administered orally and via the parenteral route to conventional rats and, orally to germ free rats. It was seen to be ineffective in germ free and parenteral rats, indicating importance of microbial activity on hydrolysing glycosides to simple sugars [8]. On the genus level, Bacteriodetes species are the most abundant and are

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mainly involved in glucosidase production, an enzyme required to breakdown amygdalin into cyanide [9].

IV administration of amygdalin showed no such effect [6]. Milazzo et al. report two studies, one employs IV administration of Laetrile and the other, application of Laetrile on tumour sites. Both show improved survival rate but not complete positive response in cancer patients [2]. No HCN toxicity was reported in either of the cases, suggesting that it is prevalent solely during oral consumption [4]. Around 80% of thiocyanate (after detoxification by Rhodanese enzyme) and some amounts of parent drug can be found in urine after IV and subcutaneous administration [10,11].

Studies have been carried out to prove the benefit of amygdalin to cancer patients but, due to conflicting results, side effects and lack of improvement on survival rate, many feel that the risk to benefit ratio for this compound is too high [2,6,12].

2. Important components of the equation

2.1. Amygdalin

A cyanogenic-diglycoside, amygdalin (D-mandelonitrile-β-D-glucosido-6-β-D-glucoside) is commonly found in stone fruits and berries like apricots, plums, peaches, apples, papaya and cherries and also in plants like rice, unripe sugarcane, sorghum, certain species of nuts and yam in combination with other cyanogenic glycosides like Linamarin [13-17]. Sometimes, it is also found in the leaves and foliage of plants like Saskatoon berries and mature trees of the Prunus taxa [13,18]. Aromatic compounds like benzyl alcohol, benzoic acid and benzenaldehyde are also commonly found in such fruits [13]. Studies show that amygdalin undergoes enzymatic hydrolysis and is converted to two glucose molecules as well as mandelonitrile, which due to its unstable nature, is spontaneously converted to HCN and benzenaldehyde, as observed in Fig. 1 [13,14,19]. This benzenaldehyde, which commonly helps impart aroma to the fruit, can be further oxidised to benzoic acid and, the HCN is capable of causing toxicity, if amygdalin is orally ingested, by inhibiting the cytochrome oxidase of the Electron Transport Chain (ETC) in the mitochondria [13,14].

Enzymatic hydrolysis of amygdalin is known to be accelerated in the presence of heat. Water also plays a role in bringing the substrate and enzyme in close proximity. An instance is in fruits like cherries where, increasing the temperature up to 65 °C, hydrolyses benzenaldehyde, due to the accelerated action of amygdalin hydrolyse, prunasin lyase, β-glucosidase, water and mandelonitrile lyase [13]. In animals, vitamin C is known to have the same effect on amygdalin, as it alternates blood cysteine levels, leading to a decrease in detoxification of HCN by decreasing Rhodanese activity [6]. Those with cyanocobalamin deficiency or genetic inability for detoxification are also prone to increased blood cyanide levels [2,6]. Clinical dose of amygdalin tobe taken should not exceed 680 mg/kg [20].

2.2. Laetrile

First synthesised by Krebs and termed as vitamin B17, laetrile is an acronym for the terms laevorotatory and mandelonitrile [2,11]. Initially utilised as an alternative cancer therapy in Russia and then in the USA, around 1920s, it was patented by the USA as D-mandelonitrile-β-glucuronide. It is also popular in Mexico but, the compound used is D-mandelonitrile-β-gentiobioside (has two glucose molecules combined through hydroxyl positions 1 and 6) [2,29]. Laetrile therapy is usually taken in combination with other CAM proponents, like diet, urine, metabolic and oral therapy, β-glucuronide injections and intake of fruit seeds [2]. Laetrile, unlike amygdalin, has only one glucose molecule [16]. It has 6% cyanide by weight. If eaten with foods that have β-glucosidase, combined with gut-flora composition, it leads to cyanide toxicity which can occur in three stages as mentioned in Table 2 [30].

2.3. Rhodanese

Mainly catalysing the formation of thiocyanate from cyanide and thiosulfate, Rhodanese (thiosulfate sulfurtransferase) is found in a variety of plants and animals (differs based on various factors such as sex, organs, diet, age and species) with properties as described in Table 3 [14,31]. It is believed that rhodanese distribution in animal tissues depends on cyanide exposure since the primary function of this enzyme is believed to be cyanide detoxification. In animals, it is found as a mitochondrial enzyme as shown by Mimori et al.on rat brain [14,31-33]. It interacts with mitochondrial membrane bound iron sulphur centres (of the mitochondrial ETC) and modulates the rate of respiration in cells [11,14,31,32]. The sulphahydryl group of the active site could form an intramolecular disulphide linkage with another of its kind but, it is hindered due to close proximity with aromatic groups [14,40]. However, these groups can form hydrophobic interactions [14]. The thiosulfate acts as a sulphur donor in HCN detoxification [11,14,31]. As seen in Fig. 2, Rhodanese transfers sulfane atoms from this donor to a thiophilic acceptor [32,42]. Sometimes, even cystine and methionine act as sulphur donors [11,31]. This detoxified HCN is excreted through the kidneys as thiocyanate [11,14,42]. Studies have reported that malignant cells are deficient in Rhodanese [2].

Table 1

| Toxicity victim | Cause, symptoms and effects |
|-----------------|----------------------------|
| 67 year old woman (1983) | Consumed laetrile tablets for cancer treatment along with bitter almonds. Led to demyelination and axonal degredation. Recovered via IV administration of sodium nitrite and sodium thiosulfate followed by hydroxocobalamin administration. |
| 28 month old girl (2011) | Unconsciousness and seizures after ingestion of 10 apricot seeds. Died after 22 days with whole blood cyanide levels of around 3 mg/L. |
| 32 year old female | Consumed amygdalin supplements. Developed systemic toxicity as well as diabetes insipicidus but, recovered with appropriate therapy |
| 4 year old child with malignant brain disease (metastatic ependymoma) | Given standard oncology therapy as well as several alternate therapies like apricot kernels, oral and IV administration of amygdalin and vitamins. Life threatening toxicity symptoms developed. Recovered in three days with thiosulfate administration. |
| 41 year old, healthy, non-smoking adult (1998) | Chowed and swallowed around 30 apricot kernels (15 g approximately). Developed initial symptoms in 20 min. Amyl nitrate via inhalation and sodium nitrite and thiosulfate via IV helped in recovery. |
| 28 year old man, vegetarian, non-smoker, non-drinker (2003) | Taking a herbal concoction with peach seed extract. Due to vitamin B12 deficiency and amygdalin presence, led to peripheral neuropathy |
| 35 year old woman, mentally ill | Consumed 20-30 apricot kernels. Suffered from the initial toxicity symptoms and was hypotensive, hypoxic and tachypnoeic. Recovered due to treatment with sodium nitrite and sodium thiosulfate followed by hydroxocobalamin administration of hydroxocobalamin aided in recovery |
| 48 year old man, was in comatose | Ingested 25 g of potassium cyanide. IV administration of hydroxocobalamin helped in recovery |
| 23 year old girl, was convulsing | Had a teaspoon of potassium cyanide. Was treated with hyperbaric oxygen along with IV administration of sodium nitrite and sodium thiosulfate |

Table 2

| Toxicity victim | Cause, symptoms and effects |
|-----------------|----------------------------|
| 28 year old woman (1983) | Consumed laetrile tablets for cancer treatment along with bitter almonds. Led to demyelination and axonal degredation. Recovered via IV administration of sodium nitrite and sodium thiosulfate followed by hydroxocobalamin administration. |
| 28 month old girl (2011) | Unconsciousness and seizures after ingestion of 10 apricot seeds. Died after 22 days with whole blood cyanide levels of around 3 mg/L. |
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2.4. β-Glucosidase

Also known as carbohydrate activating or hydrolytic lysosomal enzyme, β-glucosidase having differential properties (Table 4) releases benzaldehyde, glucose and HCN from amygdalin, which has glycosidic linkages [2,11,43]. Laetrile is broken down by β-glucuronidase due to the presence of a glucuronide group[2]. When this HCN is released, it enters the cell, inhibits cytochrome oxidase C by reacting with the ferric iron group during mitochondrial respiration, due to its ability to form complexes with metal ions and leads to cell lysis by inhibiting ATP synthesis. It can also lyse cells by destroying lysosomes due to increasing acid content[2,11,44].

Malignant cells have large quantities of β-glucosidase and β-glucuronidase (as found in urine, tissue and blood serum samples of cancer patients, and murine studies carried out by Manner et al.). Cancer cells are dominant in anaerobic glycolysis and β-glucosidase is most active in lactate induced acidic conditions[2,16,44]. This ultimately leads to the release of HCN, if amygdalin is present near the cancer cells. A study by LI Yun-long et al., using monoclonal antibodies targeting β-glucosidase and amygdalin to cancer cells showed positive cell lysis, confirming HCN and β-glucosidase activities in cancer therapy[44].

3. Gut microbial flora

Bacteria are highly diverse and dominant in the gastro intestinal tract (GIT), with around $10^{14}$ bacteria and 500 different species, dominated by the anaerobes. They are classified as three types based on their properties as given in Table 5 [52,53]. They not only play an important role in the metabolic processes and nutrient conversion but also as pathogenic factors in diseases like obesity [54]. The microbes have a microbiome which is 100 times larger than the human genome and they start growing during birth. The first week of life has aerobes that utilize oxygen and set up conditions for anaerobes. They rapidly alter due to various factors and are fully established by 4 years. The main members are the Firmicutes, Bacteriodetes and Actinobacteria which contribute to cyanide release [54].

Intestinal microbiota obtain their nutrition by hydrolysis of sulfates, amides, glucuronidases, esters and lactones through the action of enzymes that produce such as sulfatase, esterase, α-rhamnosidase, β-glucosidase and β-glucuronidase [20]. 0.16 s rRNA sequencing can be used to identify human gut microbiota [55]. A Human Microbiome Project (HMP) has been established by NIH to characterise the mammalian microbiota [56]. (Tables 6–10).

4. Prebiotics and probiotics

Prebiotics are compounds like certain lipids, proteins, carbohydrates and peptidases that help initiate specific changes in the activity and composition of the gut-microbiota, thus propagating well-being and health of the host [20]. Probiotics are organisms like Lactobacillus and Bifedobacterium, which help modulate intestinal bacterial enzymes and absorb or bind carcinogens [57–59]. They are safe for consumption...
to promote a healthy gut health and to avoid cyanide toxicity due to amygdalin breakdown. Steer et al. have shown how fructo-oligo-saccharides increase the amount of Lactobacillus and bifidobacteria in vitro [60].

5. The microbiome and orally administered amygdalin

When consumed orally, a drug is influenced by enzymes of the GIT lumen, gut wall, hepatic and gut microbiome [61]. Enzymes of the microflora, gut nucleases and lipases as well as transferases, peptidases, cytochrome P450 and proteases influence metabolism of drugs and nutrients [61]. Lower blood flow of the intestinal mucosa increases residence time of drugs in the enterocytes. Also, the brush border bound glycosidases which can cleave a glycosidic linkage, does not contribute much to the metabolism of orally administered drugs due to its requirement to bind to highly specific cleavage sites [61]. These two factors are what are responsible for the lack of germ free animals to lead to cyanide toxicity on oral administration of amygdalin. Two mammalian β-glucosidases found in the mucosa of the brush border in the intestine is Lactasephlorizin hydrolase (LPH) and cytosolic β-glucosidase (CBG), which can also act on bile and fatty acids to produce carcinogens [62,63,90]. Due to low intestinal enzymatic activity, the compounds that do not act as substrates go down to the colon and are acted upon by the gut microbial enzymes.β-glucosidases present in kernels are also responsible for amygdalin hydrolysis [4].

The gut microbial flora also determines the degree of toxicity and whole blood cyanide levels [21]. They have high β-glucosidase activities, predominantly the Bacteriodetes, and release cyanide via symbiotic digestion of Amygdalin [4].

It has been shown that the intestinal and microbial β-glucosidases have different substrates. Antibiotic treatment has shown a decrease in gut-flora but, when given amygdalin, only prunasin and no HCN was found. This shows that intestinal enzymes hydrolyse amygdalin only to prunasin, which goes down to the colon, is acted upon by the microbial β-glucosidase and completely hydrolysed [4]. The gut microbiota is difficult to quantify with conventional techniques, making it hard to find the consortium of each individual and speculate on individual dose toxicity and efficacy [65]. Zhang et al. found that the gut microbiota of a polysaccharide consuming termite predominantly had members of the Bacteriodetes species. They were found to be a rich source of β-glucosidase genes. It was shown that even in the human gut, Bacteriodetes produce β-glucosidase enzyme, which plays an important role in hemicellulose or cellulose degradation due to its function as a cellulose hydrolase [43]. In fact, studies on germ free and control rats have shown that the gut microbiome leads the host to increase glucose and tri acyl glycerol production [36]. This could explain why amygdalin is actively hydrolysed, due to its glucose content.

It has been observed in obese and non-obese patients, that with an increase in body weight, Bacteriodetes to Firmicutes ratio decreases although, Dumah et al. and Zhang et al. found no difference in the ratio [20,54,66]. High fibre diets like those in Europe and rural Africa show a good Bacteriodetes population in the gut [66]. This suggests that interactions between diet, immune system, gut microbiota and metabolism have great impacts on health as well as metabolic activity of the bacteria [20]. Lactulose, a commonly used prebiotic, is also known to decrease the amount of β-glucosidase producing Bacteriodetes [20].

![Fig. 2. Detoxification of cyanide in the body via action of Rhodanese enzyme [14,41].](image-url)
Table 4
Properties of β-glucosidase [2,11,21,24–51].

| Properties                  | Bacteriodeses | Actinobacteria |
|-----------------------------|---------------|----------------|
| Molecular weight            | 40–250 kDa    | 3.5–5.5, most active at 5 |
| pH                          |               |                |
| Main function in plants and animals | To cleave the β glycosidic bond between aryl and saccharide groups (1,4, 1,2 and 1,6) thereby releasing glucose. |
| Location                    |               |                |
| Inhibition assays in vitro  | Cellulobiomadase |                |
| Activation assay in vitro   | (CBR), glucosylphosphingosine and fluoromethyl cellobiose (FMCB) |                |
| Commercial uses             | Use of bile acids along with cholic acid |                |

Table 5
Classification and properties of the gut microbes [20,54].

| Firmicutes                  | Bacteriodeses | Actinobacteria |
|-----------------------------|---------------|----------------|
| Gram positive               | Gram positive | Gram positive  |
| Dominant in large intestine | Dominant in large intestine | Dominant in large intestine |
| 64%                         | 23%           | 3%             |
| Detected via RNA sequencing | Detected via RNA sequencing | Detected via FISH |
| Anaerobic                   | Anaerobic     | Anaerobic      |

Table 6
Factors affecting gut microbial composition [20].

| Mode of infant delivery     | Activating | Inhibiting |
|-----------------------------|------------|------------|
| Antibiotic exposure         |            |            |
| Neonatal and adult nutrition|            |            |
| Stress                      |            |            |
| Age                         |            |            |
| Degree of hygiene           |            |            |
| Genetic factors             |            |            |
| Mother's genetic make-up    |            |            |

Table 7
Types of Digestion [64].

| Type of Digestion            | Description |
|------------------------------|-------------|
| Genuine Digestion            | Performed mainly in the stomach by the organisms own enzymes. |
| Autolytic Digestion          | Occurs due to the food's own enzymes. |
| Symbiotic Digestion          | Takes place due to the metabolic activity of the symbiotic microbes within the host organism. |

Animal studies have shown a decrease in β-glucuronidase levels on consumption of probiotics containing Lactobacillus and Bifidobacterium supplements, thus indicating a decrease in levels of β-glucuronidase encoding Bacteriodeses species [57,64]. Studies have shown a lower activity of β-glucosidase and β-glucuronidase in Lactobacillus and Bifidobacterium as compared to Bacteriodeses [67]. A DMH model was used to show a decreased activity of both the enzymes in case of Lactobacillus Acidophilus and Lactobacillus GG, while it showed increased activity for Bacteriodes fragilis, which has the highest β-glucosidase activity [4,67]. Older people tend to have high levels of Lactobacillus, enterococci, clostridia and enterobacteria compared to other microbes [68]. Ravcheev et al., used comparative genomic studies for Bacteriodeses thetaotaomicron and showed the presence of 269 glycoside hydrolases, with glucuronidase and glucosidase genes also present [9,69]. Patel and Goyal showed that administration of nutritionally rich foods like CAM30 or blackcurrant extract lead to a decrease in Bacteriodeses content as well as levels of β-glucosidase, proving again the production of this enzyme mainly by this particular phylum [70]. Karlsson et al. have reported that gut Bacteriodeses species are restricted to closely related species of Bacteriodeses fragilis and are abundant in carbohydrate acting enzymes [71]. Lactobacillus species are also known to produce good amounts of β-glucosidase enzyme.

Table 8
Evidence showing how gastrointestinal flora maximizes cyanide toxicity [11,54].

| Research experiment                  | Observations and results                      |
|--------------------------------------|------------------------------------------------|
| Veibel (1950) and Hildebrand and Schroth (1964) | Showed high β-glucosidase production in various bacterial strains |
| Reinmauer (1972), IV and oral administration of amygdalin to mice | 69.3% of IV and 19.3% of oral doses were obtained unconverted in the urine |
| Greenberg (1975)                     | Greenberg et al. will be excreted almost unchanged on parenteral administration |
| Carter et al. (1980), fed germ free and conventional rats daily doses of 600 mg/kg of amygdalin | Excerted almost completely unchanged |
| Greenberg (1975)                     | None of the effects of cyanide toxicity were observed in the germ free rats, with large amounts of unconverted amygdalin obtained in feces. Conventional rats showed high blood cyanide levels, thiocyanate levels and death within 2-5 h |
| He reports that it is believed that body tissues produce low quantities of β-glucosidase which is why parenteral administration leads to excretion of mainly unconverted amygdalin while, due to gut microbial glucosidase activity, cyanide toxicity can occur |
that help enhance dietary and sensory properties of fermented foods and also play a valuable part in interaction with the host [59]. However, studies have shown that excess bioavailability of dietary toxins and xenobiotics is also common due to this enzyme released by LAB [59]. These effects could be taken into consideration to form conditions under which toxicity is prevalent and ways in which the consortium could be altered to tackle poisoning due to amygdalin. This could lead to administration of safer oral doses, after determination of an individual’s consortium through faecal studies.

Amygdalin is used as a CAM therapy because, the cyanide obtained on hydrolysis will bind to cytochrome oxidase c and a3, hinder respiration and DNA synthesis due to formation of reactive oxygen species, block nutrition source of cells and lead to lysis [16,53,72,73]. This is useful on parenteral administration but, on ingestion, it reaches the gut unchanged. The gut microbiota is anaerobic and produces high levels of lactic acid via fermentation of pyruvate (anaerobic metabolism) [74]. This pH increases activity of β-glucosidase due to which amygdalin is hydrolysed to cyanide and leads to toxicity. However, R.A. Blaheta et al. have shown that in the absence of β-glucosidase, amygdalin still has anti-tumour properties, giving rise to the possibility that it is not the cyanide that is responsible for that effect [4]. Vitamin C, a water soluble vitamin, is also commonly administered as a CAM therapy for cancer as well as diseases like Epilepsy [93]. It is believed to increase the strength of the intracellular matrix in which cancer cells are embedded, by inhibiting collagenase and hyaluronidase, which weaken the matrix and lead to benign tumors [75,76]. These two CAM therapies are usually administered together. Now large doses of Vit C weaken the matrix and lead to benign tumors [75,76]. These two CAM therapies are usually administered together. Now large doses of Vit C are known to deplete cysteine stores of the body. Cysteine plays a role in the rate limiting step of thiocyanate formation [74]. Amygdalin will be hydrolysed by gut microbes, and coupled with the physiological effects of Vitamin C, lead to accelerated cyanide toxicity [77]. Studies by Backer et al., prove the same [78]. Studies have given conflicting results for use of both the therapies alone and in combination. Some results for use of both the therapies alone and in combination. Some studies have given conflicting results for use of both the therapies alone and in combination. Some studies have given conflicting results for use of both the therapies alone and in combination. Some studies have given conflicting results for use of both the therapies alone and in combination. Some studies have given conflicting results for use of both the therapies alone and in combination. Some studies have given conflicting results for use of both the therapies alone and in combination. Some studies have shown that the cyanoglycoside while, in-vivo studies do not offer the same. The antibody directed study has paved way for a safer method to deliver amygdalin but, animal and clinical studies are required before therapeutic use. Conflicts also arise due to cases such as that reported by R.A. Blaheta, that document no signs of cyanide toxicity for a patient consuming twice his dose of laetrile tablets. Current literature points to the fact that amygdalin causes toxicity on oral consumption and not IV administration but, its mode of action and toxicity causing dose is still not confirmed. Variable amounts of oral doses cause toxicity in each case and this can be attributed to an ecletic gut consortium. There is no definite way of pointing out each individual’s microbial consortium and providing a safe oral dose. Such unresolved and conflicting facts make way for a broad avenue of research for a compound that could in-fact be the next step in cancer therapy.

Transparency document. Supporting information

Supplementary data associated with this article can be found in the online version at http://dx.doi.org/10.1016/j.bbrep.2018.04.008.

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