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Review Paper

Non-conventional Beverages: Emerging Biotherapeutics

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ABSTRACT

The resurgence of interest in natural therapies has sparked a renaissance in the utilization of non-conventional beverages as emerging biotherapeutics. Sourced from a variety of plants, animals, and minerals, these beverages provide a plethora of bioactive compounds, each with unique physiological impacts. This review explores the scientific foundation underpinning the therapeutic potential of non-conventional beverages, encompassing alcoholic, teas and other miscellaneous beverages. Through an examination of their bioactive compounds, including polyphenols, flavonoids, peptides, vitamins, and minerals, the article elucidates their interactions with biological pathways and cellular processes, highlighting their potential in preventing and managing various health conditions. By consolidating existing knowledge and exploring novel beverages, this review underscores their role as promising agents in the quest for improved human well-being, highlighting their importance in natural therapies and health promotion. This review explores the scientific foundation underpinning the therapeutic potential of non-conventional beverages, encompassing categories such as alcoholic beverages, teas, and other miscellaneous beverages.

Keywords: Non-conventional beverages, Alcoholic beverages, Teas, Miscellaneous beverages

The practice of using natural substances obtained from plants, animals, and minerals to treat illnesses predates modern medicine, dating back to the Paleolithic era. Over time, the popularity of natural therapies declined with the emergence of modern treatments. In today's context, the introduction of new chemical treatments has revealed potential adverse effects associated with these traditional remedies. Consequently, scientific focus has shifted back to ancient, natural agents of treatments, encompassing the use of the natural agent itself, natural agent-derived extracts, or food as therapeutics (Cuamatzin-García et al. 2022; Carboni *et al.* 2023).

Non-conventional beverages from natural sources have demonstrated functionality in terms of health benefits. Examples include alcoholic, teas and other miscellaneous beverages. The therapeutic properties of these drinks are credited to phytochemicals and various other bioactive compounds, making them medically relevant. Intake of antioxidant-packed beverages such as fruit juices, red or white wine, green tea, or coffee has been linked to the prevention of breast cancer in women (Hirvonen *et al.* 2006). Fig. 1 illustrates the potential mechanisms by which these beverages confer preventive and therapeutic capabilities against major diseases.

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Today, the consumption of non conventional beverages has become a firmly established practice, fueled by consumer interest in products touting health advantages. Interestingly, the incorporation of these non conventional beverages into human diets dates back to antiquity, initially aimed at extending the shelf-life of perishable materials. At the core of non-conventional beverages as emerging biotherapeutics lies a robust scientific foundation rooted in the intricate understanding of the bioactive compounds they contain and their physiological influence. As exploration delves further into sensory experiences and technological advancements, a novel horizon comes into view - the quest to craft items that not only captivate the senses but also promote human welfare. Within this context, the global market for producing zero- and low-ethanol beverages is burgeoning, with efforts directed at overcoming obstacles related to availability, acceptability, and affordability – persistent challenges that await effective solutions (World Health Organization, 2023; Brugnoli *et al.* 2023).

Non-conventional beverages, known for their versatility in addressing health concerns, are increasingly embracing unconventional ingredients and formulations. Alongside traditional fortified beverages, there's a notable trend towards non-conventional options, such as "beauty beverages" containing collagen and collagen hydrolysates, touted for their skin health benefits. The global beauty drink market, which stood at USD 700 million in 2016, was projected to reach USD 1.3 billion by 2023, boasting an impressive estimated CAGR of 11.8%.

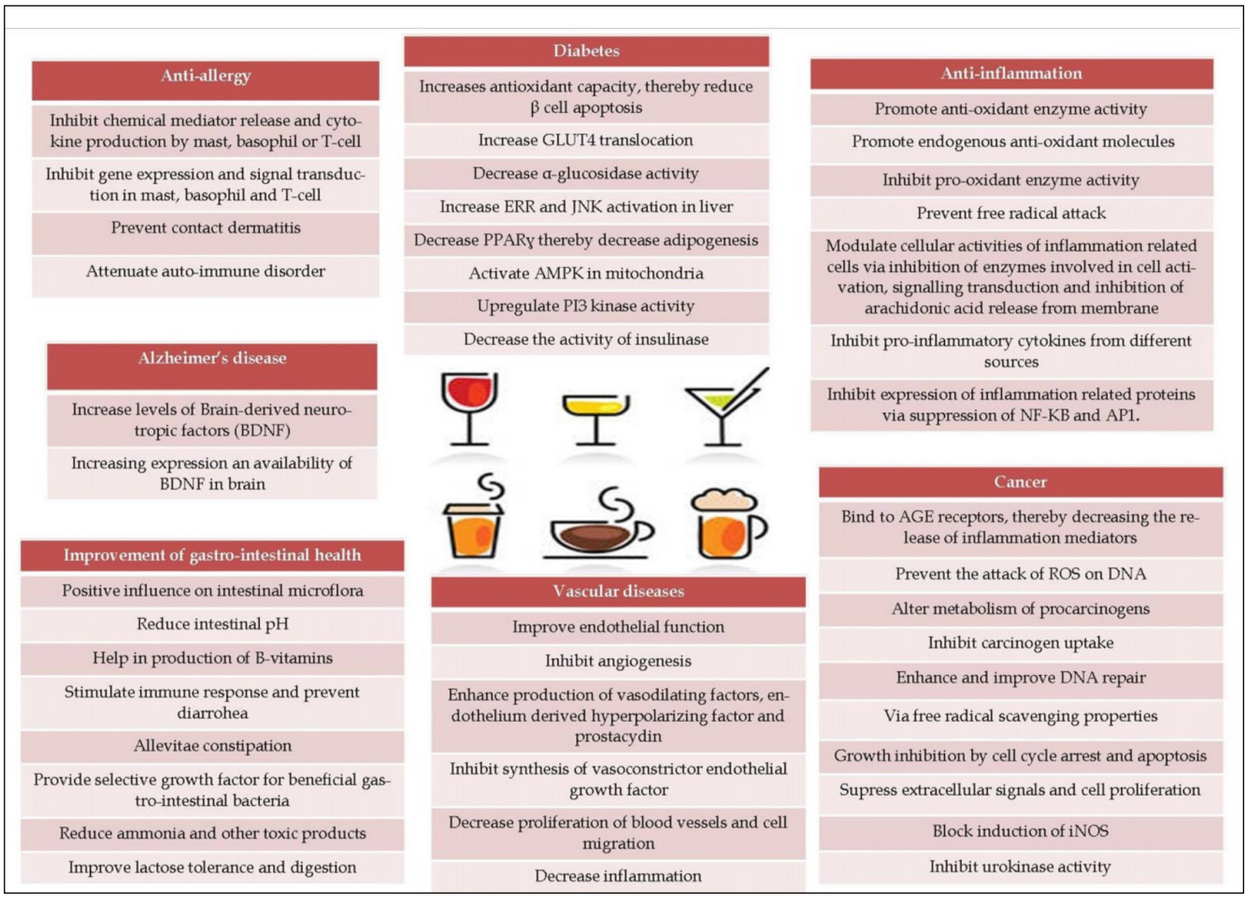

Fig. 1: The potential preventive and curative abilities of non-conventional beverages against major diseases

This expansion isn't limited to traditional sectors; it's also reshaping non-conventional beverage categories. Moreover, consumers are displaying a heightened interest in organic ingredients across all beverage types, while simultaneously expressing growing skepticism toward artificial additives like food colorings and sweeteners. This shift offers manufacturers opportunities to differentiate their products by incorporating natural ingredients with documented health benefits (Nazir *et al.* 2019). This review article consolidates wide range of scientifically assessed non-conventional alcoholic, teas and other miscellaneous beverages. The scientific foundation of non-conventional beverages as emerging biotherapeutics lies in the understanding of bioactive compounds and their impact on human health. These naturally occurring substances exert specific physiological effects, ranging from antioxidant and anti-inflammatory properties to immune modulation and gut health improvement. Common bioactive compounds found in non-conventional beverages include polyphenols, flavonoids, peptides, vitamins, and minerals. These compounds engage with biological pathways and cellular processes, potentially aiding in the prevention and control of various health conditions. The study not only fills existing gaps but also investigates novel non-conventional beverages and the complex interplay of bioactive compounds and metabolites that exhibit promising therapeutic properties.

Methodology

PubMed and Google Scholar searches unveiled that the discussion on innovative non-conventional beverages, coupled with the intricate interplay of bioactive compounds and metabolites displaying promising therapeutic potentials, remains relatively unexplored in the literature. To delve into this topic, we implemented a well-defined schematic search strategy across various internet sources, including review articles and research papers, aiming to unearth scientifically evaluated non-conventional alcoholic beverages, teas, and other miscellaneous beverages. Our search keywords were closely aligned with terms related to alcoholic beverages, teas, and their specific physiological effects, encompassing antioxidant and anti-inflammatory properties, immune modulation, and gut health enhancement. Despite our efforts, the available data on this subject matter proved to be exceedingly scarce. Our search, employing the aforementioned keywords, yielded approximately 20-30 articles, beyond which the findings became either unrelated or repetitive. This literature review underscores the absence of any comprehensive coverage of this collective data, thus presenting an intriguing research opportunity in the realm of "Non-conventional beverages: Emerging biotherapeutics." Categories that are gaining global interest include alcoholic beverages, teas, and miscellaneous beverages (Brugnoli *et al.* 2023), and these are discussed hereafter. Furthermore, we highlighted various challenges encountered, including regulatory complexities, ensuring safety and efficacy, consumer education, and the advancement of scientific methodologies. Addressing these gaps could pave the way for the development of effective and widely accepted biotherapeutic beverages, thereby enhancing human health and well-being.

Alcoholic beverages

Alcoholic beverages defined as those containing an alcoholic content of 0.5% or higher, encompass a diverse array of fermented, distilled, and integrated drinks. In recent years, consumer interest in alcoholic beverages has surged, largely driven by the allure of their unique flavors (Zhou *et al.* 2024). Various factors, including the quantity consumed, serving apparatus, and serving temperature, significantly influence consumers' perception of alcoholic beverage flavor. Remarkably, the geographical origins of alcoholic beverages are deeply intertwined with the countries or regions where they are crafted (Tamang *et al.* 2020).

Dating back to ancient times, the historical roots of alcoholic beverages are rich and varied. The earliest known reference to a potentially medicinal alcoholic brew dates back to China's Neolithic site of Jiahu around 7,000 B.C., where biomolecular archaeological

analyses unveiled a concoction produced from rice, honey, a Chinese grape variety, and hawthorn tree fruit (McGovern, 2010). Derived from sources such as sweet fruits, honey, and saccharified cereals, alcoholic beverages have long held significance (McGovern, 2009).

Alcoholic beverages are crafted through the process of alcoholic fermentation of sugar-containing liquids. Sugars fermentable by yeasts are either naturally present or generated through processing methods like the hydrolytic cleavage of starches and dextrins, yielding simple sugars. Among the most renowned alcoholic beverages are beer, wine, and brandy. Beer and wine, with their longstanding industries, were familiar to ancient civilizations, whereas the distillation process for liquor production emerged much later in history. Ethanol, the primary component in alcoholic beverages, boasts a high nutritional energy value of 7 kcal/g (Cloetens and Ellegård, 2023).

Historically, alcohol served as a universal remedy, offering evident health benefits such as pain alleviation, disease regulation, and microbial action against waterborne pathogens. The moderation in consumption of alcoholic beverages is believed to provide a plethora of benefits to humans. The concept of 'medicinal wine,' documented in various pharmacopoeias worldwide, highlights alcoholic beverages' potential analgesic, antibacterial, and psychotropic qualities. Alongside conventional alcoholic beverages, non-conventional varieties like herbal alcoholic beverages, incorporating herbal beer, wine, and spirits, add to the diversity of options available to consumers.

Herbal alcoholic beverages

Herbal alcoholic beverages, typically consisting of ethanolic or hydroethanolic extracts from herbal materials (Ogbonnia *et al.* 2010), hold a prominent place in African culture, Southeast European, and Mediterranean regions. Herbal beverages are made in Malaysia based on personal experiences, observations, and rituals rooted in socio-religious ideas that have been passed down from generation to generation (Sooi and Keng, 2013; Shaik *et al.* 2023). These drinks are generally produced from the natural ingredients of different morphological plant parts, namely leaves, stems, roots, fruits, buds, and flowers, which have long been consumed through generations (Shaik *et al.* 2023). Nowadays, research on herbal beverages receives less attention, resulting in a lack of understanding regarding their benefits. These beverages, in the form of spirits and liquors, are deeply ingrained in local gastronomy (Komes *et al.* 2012) and primarily intended for oral consumption. They incorporate herbal components that bestow varying degrees of medicinal impact contingent upon the specific type and quantity used during preparation (Kumadoh and Ofori-Kwakye, 2017). Furthermore, the inclusion of alcohol in production serves to confer a preservative attribute, extending the shelf life compared to decoctions and infusions (Buglass, 2011). The qualities of herbal liqueurs, encompassing antioxidant, antibacterial, and antifungal properties, alongside total phenolic and flavonoid compounds, are influenced by storage conditions and duration (Karabegovic *et al.* 2012). As such, the exploration of herbal alcoholic beverages not only unveils their cultural significance but also underscores their potential as functional beverages with diverse health-promoting properties.

Herbal wines

The most reviewed herbal alcoholic beverage with known remedial effects is wine, a common alcoholic beverage made mostly from grapes undergoing partial or full alcoholic fermentation. In recent times, significant efforts have been made to explore inventive approaches aimed at amplifying preferred tastes and aromas in wine, offering a strategic advantage in the worldwide market. Regulations governing the utilization of flavor additives in industrial wine manufacturing are rigorously enforced across most wine-producing countries. Depending on the proportion of wine incorporated as a flavor enhancer, it might be categorized as either a "wine product" or a "fruit wine" (Liang *et al.* 2021).

Many fruits, other than grapes, can be used for making wines (Soni *et al.* 2021). Several studies have exploited remedial herbs for wine production, using herbs either as a substrate or as adjuncts. The use of herbs in winemaking is not new. Chemical analysis of pottery jars from around 3150 B.C. revealed the existence of historic organics absorbed into the jars, including a variety of natural products—specifically, plants and tree resin discharged during grape wine production. These findings provide chemical proof that ancient organics can be used as therapeutic therapies, showing how, for millions of years; people worldwide have used their natural environment to find efficient herbal medicines. The active ingredients of these herbs have only just begun to be separated using modern analytical techniques (McGovern, 2009). These herbs possess antioxidant and bacteriostatic or bactericidal activity, prolonging the storage life of foods and beverages (Panda *et al.* 2014). Additionally, they supplement foods with essential minerals, vitamins, and phytonutrients.

Wines demonstrate the protective effects against various diseases, including diabetes, ischemic heart disease, cancer, Alzheimer's disease, inflammation, and infections, in addition to oxidative stress (Boban and Modun, 2010; Snopek *et al.* 2018). The substrate from which wines are made contains a significant amount of polyphenolic and other bioactive compounds that impart medicinal properties to the wines. Resveratrol, one of several naturally occurring polyphenolic compounds found in grapes used in wine production, is of particular importance and has been linked to low mortality. Combining resveratrol with antibiotics may potentially increase the antibiotic efficacy of certain classes of antibiotics (Vestergaard and Ingmer, 2019). Significant advancements have been achieved in the technological aspects of crafting diverse wines, encompassing grape-based varieties as well as non-grape alternatives derived from fruits such as mango, apple, peach, plum, cashew-apple, pineapple, pomegranate, strawberry, and kinow (Karagiannis, 2011).

These herbal wines have also been studied for therapeutic purposes through in-vivo research. *Aloe vera* wine, when tested in an animal model of *Salmonella typhimurium*, inhibited the organism's growth and improved oxidative stress status. Aloe-amla wine has also been found to improve the redox status and inhibit *Salmonella* infection in mice (Trivedi *et al.* 2012; Trivedi *et al.* 2015). Sea buckthorn wine, with a better phytonutrient status compared to grape wine, arrested phorone-induced hypercholesterolemia in mice and improved their redox status (Negi *et al.* 2013). Administration of pineapple wine for three months proved to be an immune booster for male Wistar rats, with no observed harmful effects on the liver when taken in moderation (Ajani *et al.* 2012). Additionally, in-vivo evaluation of multi-fruit wine from tomato, orange, lemon, African star apple, and almond suggested that phytochemicals and certain wine additives might influence the hematological parameters of animals (Asuk *et al.* 2013). Yakju, Korean rice wine, has been found to block the progression of B16L6 mouse melanoma and HRT18 human colon adenocarcinoma cells *in-vivo* (Chung *et al.* 1998). A study revealed that Chinese rice wine reversed the oxidative damage caused by D-galactose in aging mice (Liu *et al.* 2020). Even bakeries fortified with fruit and herbal wines possess anti-mutagenic properties *in-vivo* via enhanced detoxification and reduction in nitrosomethylurea formation (Pratoomwun and Kangsadalampai, 2008). These wines, derived from fruits and herbal plants, containing hundreds of medicinal compounds, exhibit curative properties, including polyunsaturated fatty acids, anthocyanins, flavanols, essential oils, proanthocyanidins, and phenolics. Apart from their role as antioxidants, these compounds provide anti-inflammatory, anti-mutagenic, and antimicrobial properties (Maksimović and Maksimović, 2017).

An ancient Chinese herbal wine called Chang, containing two aromatic compounds, namely camphor and cedrene, along with acetic acid, benzaldehyde, and short-chain alcohols distinctive of rice and grape wines, has shown effectiveness against colon cancer, lung cancer, ascetic liver tumor, malaria, hepatitis B and C, uveal melanoma, Kaposi's sarcoma, hepatoma, ovarian cancer, neuroblastoma,

pancreatic cancer, and myeloid leukemia (McGovern *et al.* 2010). In a study conducted in male LACA mice, Negi *et al.* (2013) investigated the preventive benefits of sea buckthorn wine towards phorone-induced oxidative stress and high cholesterol diet-induced hypercholesterolemia. An in vivo study exploring the antioxidant capability of mulberry and jamun wine showed a reduction in oxidative stress in streptozotocin-induced diabetic wistar rats (Srikanta *et al.* 2016). Swami (2016) prepared non-traditional wine variants from different parts of *Syzygium cumini* and assessed the medicinal efficacies against diabetes mellitus, dyslipidemia, atherogenesis, and associated oxidative stress in a rat model. The wines had an antioxidant impact on oxidative stress, and the presence of pharmacologically active compounds restored biochemical markers of stress to normality, making the produced wines serve as both preventative and curative medications for free radical-induced chaos in diabetics (Swami *et al.* 2016; Swami *et al.* 2017). Flavonoid chemicals (flavonols, monomeric catechins, proanthocyanidins, anthocyanins, anthocyanidins) and non-flavonoid phenolic compounds (resveratrol), along with their metabolites, are abundant in grapes and products derived from these metabolites. A study by Yu (2020) explored the beneficial effects of wine prepared from blueberries, aiding in the cure of cardiovascular disease, cancer, and diabetes. Although many wines are produced, the scientific validation of the medicinal attributes of only a few of them has been reported (Table 1). Extensive research is required to validate the potentials of these herbal beverages and increase their popularity as well as market value.

Herbal beers

The ancient roots of intentional beer production, incorporating a variety of ingredients and herbs, can be traced back to ancient China, particularly within the Yangshao culture, spanning from 5,000 to 3,000 BCE. During this period, beer was crafted primarily from rice and broomcorn millet, with supplementary elements such as *Panax ginseng, Lingusticum wallichii, and Zingiber sp.* incorporated to enhance the brew's complexity (Aouizerat *et al.* 2019; Liu *et al.* 2019). Similar discoveries of early beer production emerged globally, including Anatolia during the pre-ceramic neolithic epoch and Mesopotamia and Egypt around 3,500 BCE (Rodzińska-Nowak, 2021; Nelson, 2005). Most herbal beers exhibited greater antioxidant capacity compared to traditional beers. The overall polyphenol content in herbal beers ranged from 250.8 to 1063.5 mg/L, surpassing that of conventional beers (179.2–308.4 mg/L). Notably, free phenolic acids (3.151–26.469 mg/L) such as gallic acid (0.248–2.853 mg/L), chlorogenic acid (0.422–6.420 mg/L), vanillic acid (0.567–10.256 mg/L), and caffeic acid (0.422–10.093 mg/L) were prominent in herbal beers, contributing significantly to their robust antioxidant properties (Lin *et al.* 2024).

In 2017, a unique bronze bucket dating back to the ninth century BCE was unearthed near Kladina village in the Czech Republic. This artifact, positioned as a "transition type" between the Late Bronze Age and the Hallstatt Period, underwent meticulous palynological assessment and gas chromatography/mass spectrometry analysis. The findings suggested that the bucket might have contained a millet-based sustenance or libation, augmented by the inclusion of herbaceous components such as bitter-sour herbs (Jilek *et al.* 2022). Herbal beers, offering pharmacological properties, have diverse recipes and are available commercially (Table 1). For instance, a beer composed of skullcap, kava kava, St. John's wort, and passionflower is known for its beer-like characteristics without the numbing effects of alcohol, providing a soothing impact on the drinker (Gruenwald, 2009). Another patented herbal beer from the plant *Andrographis*, developed by Pushpagandan *et al.* (2012), possesses medicinal properties, including choleretic, anti-oxidant, nervine relaxant, cardio-tonic, diuretic, digestive, and immunomodulant effects.

Marula (*Sclerocarya birrea*) is a medicinally important plant, and its fruits are traditionally brewed into a beer with reported medicinal properties, particularly against bacterial infections (Fundira *et al.* 2002; Komolafe, 2014). Pluháčková *et al.* (2020)

Table 1: Validated medical potencies of non-conventional herbal wines and beers

Beverage	**Disease**	**Reference**
	Herbal Wines	
Aloe vera wine	*Salmonella typhimurium* infection, Oxidative stress	Trivedi *et al.* 2012
Aloe vera-amla wine	*Salmonella typhimurium* infection, Oxidative stress	Trivedi *et al.* 2015
Seabuckthorn wine	Hypercholestrolemia, Oxidative stress	Negi *et al.* 2013
Chinese Rice wine	Oxidative stress	Liu *et al.* 2020
Korean rice wine	Melanoma, Human colon adenocarcinoma	Chung *et al.* 1998
Pineapple wine	Immune booster	Ajani *et al.* 2012
Blueberries wine	It can aid in the prevention of cardiovascular disease, cancer, and diabetes.	Yu, 2020
Syzygium cumini wine	Anti-oxidant impact	Swami *et al.* 2016; 2017
Grape wine	Breast cancer chemotherapy	Ferraz da Costa *et al.* 2020
Buckthorn wine	Reduction of oxidized glutathione levels	Negi *et al.* 2013
	Beers	
Marula (*Sclerocarya birrea)* beer	Against pathogens like *Pseudomonas aeruginosa, Staphylococcus aureus, Escherichia coli, and Enterococcus faecalis*	Fundira*et al.* 2002; Gruenwald, 2009; Komolafe, 2014
Beers with Czech Medicinal Herbs and Plants	Increased content of polyphenols and phenolic acids (more than four times in linden and plantain beer), essential oils and other substances	Pluháčková *et al.* 2020
Roselle beer	Higher levels of flavonoids, including catechol, epicatechin, and quercetin	Lin *et al.* 2024
Jasmine beer	Higher levels of flavonoids, including catechol, epicatechin, and quercetin	Lin *et al.* 2024

supplemented beers with ethanol extracts of herbs, such as ribwort plantain, small-leaved linden, purple coneflower, chamomile, and sage, enhancing the beer's phenolic compounds and essential oils content. Additionally, Lin *et al.* (2024) explored the impact of herbs on the antioxidant capacity of beer, revealing that herbal beers exhibited superior antioxidant capabilities compared to traditional beers, with roselle beer and jasmine beer displaying the most potent antioxidant effects due to elevated flavonoid content. The historical roots of herbal beer production, coupled with contemporary research on the pharmacological properties and antioxidant capabilities of herbal beers, showcase the diverse and fascinating evolution of this beverage.

Herbal spirits

Herbal spirits are typically crafted by blending herbal extracts with agricultural spirits. Imark *et al.* (2000) conducted an evaluation of the antioxidant capabilities of herbal spirits, comparing them with red wine and purified natural antioxidants like quercetin, catechin, ascorbic acid, eugenol, and trans-resveratrol. Surprisingly, the study revealed that herbal spirits exhibited higher antioxidant richness than red wine. In East-Southern Spain, herbal spirits are widely embraced, with *Thymus vulgaris, Micromeria fruticosa, Rosemarinus officinalis, and Marticaria recutita* standing out as major herbs used in their production (Martínez-Francés and Ríos, 2005). The addition of cocoa to herbal liquors has also been

reported to enhance their antioxidative properties, polyphenolic profile, and sensory attributes. This finding highlights the potential for additional enhancement of herbal spirits, potentially increasing their therapeutic effectiveness (Komes *et al.* 2012).

Teas

Tea's reputation for fragrance and therapeutic benefits has been bolstered by the ongoing development of functional foods, attracting considerable attention. Recent years have witnessed a surge in herbal tea sales across Asian countries. Varieties such as daisy, jasmine, lavender, rose, sweet osmanthus, lemongrass, and rosemary exhibit notable antioxidant and NO suppressing activities, potentially aiding in oxidative stress-associated conditions like infection, inflammation, cancer, diabetes, and renal disease (Tsai *et al.* 2007). The utilization of herbal teas for medicinal purposes spans the globe and the validated medical potencies of herbal teas are listed in Table 2. Indigenous North Americans historically brewed Canada yew needles (*Taxus canadensis*) for arthritis relief, a practice documented by European explorers (Blouin, 2004). Research has unveiled thousands of miRNAs in herbal tea, potentially serving as hidden bioactive ingredients with chemotherapeutic properties. Utilizing *Spergularia rubra* extract, one study developed an iced tea base herbal beverage rich in phenolic compounds and organic acids, offering significant benefits against Alzheimer's disease and cholinesterase inhibition (Oliviera *et al.* 2013; Li *et al.* 2016).

In Africa, rooibos tea, also known as the long-life tea, derives from the plant *Aspalathus linearis*. African women traditionally employ rooibos to alleviate heartburn and nausea during pregnancy and to soothe colic in infants due to its iron content. Rooibos stands out for its mineral, vitamin, and antioxidant richness, as well as its distinct lack of caffeine. It boasts high antioxidant levels, surpassing green tea by 50 times, and a characteristic sweet flavor, rendering it a compelling and valuable beverage. Since 1979,

Table 2: Medical potencies of herbal teas

Tea	Country	Disease controlled	Reference
Echinacea	America	Cold or flu symptoms	Lindenmuth & Lindenmuth, 2000
Green tea	China	Esophageal cancer	Gao *et al.* 1994
Hibiscus sabdariffa	North Africa and Southeast Asia	Hypertension	Faraji & Tarkhani, 1999
Peppermint, chamomile, dandelion	Dunedin, New Zealand	Effect on hepatic drug-metabolizing enzymes	Maliakal & Wanwimolruk, 2001
Mentha piperita L.	Europe	Anti-microbial, analgesic, chemopreventive and immunomodulating	McKay & Blumberg, 2006
Aspalathus linearis	South Africa	Against *Herpes simplex, Verruca plana juvenilis, Verruca vulgaris, Psoriasis vulgaris*, Anti-oxidant	Joubert *et al.* 2008; Hong *et al.* 2014
Salacia reticulate	Sri Lanka	Type 2 diabetes	Jayawardena *et al.* 2005
Plantago lanceolata	Italy	Anti-microbial	Ferrazzano *et al.* 2015
Yi-Fey Ruenn-Hou (YR)	China	Cytokine modulation	Lin *et al.* 2004
Cassia auriculata	India	Anti-diabetic	Doshi *et al.* 2011
Cyclopia	South Africa	Anti-oxidant, anti-cancer, Against *Oesophageal papillomas,* anti-aging	Joubert *et al.* 2008; Im *et al.* 2014
Ginseng	South Korea	Anti-cancer	Yun & Choi, 1990
Fuzhuan tea	China	Promotes *Pseudomonas putida* growth	Liu *et al.* 2022

Rooibos has been extensively researched for its anti-cancer, anti-aging, antimicrobial, anti-mutagenic, and lipid peroxidation inhibitory properties, both in laboratory settings and in living organisms. (Joubert *et al.* 2008).

Herbal teas derived from *Cistus* spp. have long been employed in folk medicine for their anti-spasmodic, anti-inflammatory, and antibiotic properties. Recent investigations into *Cistus incanus* tea's effects on healthy volunteers revealed a reduction in risk factors associated with atherosclerotic cardiovascular disease. Polyphenolic acids and flavonoids present in the herbal tea were found to mitigate oxidative stress and dyslipidemia, suggesting regular consumption may prevent atherosclerotic cardiovascular disease (Kuchta *et al.* 2021). Yerba maté, a traditional tea with a long history, boasts a high nutritional profile, including vitamins A, C, E, B1, B2, niacin, B5, potassium, magnesium, phosphorus, calcium, chromium, manganese, iron, selenium, and zinc. It also contains bioactives such as carotene, chlorophyll, flavonols, fatty acids, polyphenols, antioxidants, tannins, inositol, trace minerals, pantothenic acid, and amino acids (Heck and deMejia, 2007). Studies have shown its chemopreventive and antidiabetic properties in mouse models (Kang *et al.* 2012).

Traditional medicinal uses of South African teas honeybush (*Cyclopia* sp) and bush (*Athrixia phylicoides*) include expectorant effects in chronic catarrh, pulmonary tuberculosis, and treatment of various skin conditions. Research has unveiled their potential as hepatoprotective, anticarcinogenic, antimutagenic, anti-aging, anti-hemolytic, anti-allergic, and antispasmodic agents (Joubert *et al.* 2008). Fuzhuan tea, an ancient Chinese tea, has been found to promote the growth of *Pseudomonas putida* in recent studies (Liu *et al.* 2022). Kombucha, a sweetened probiotic tea fermented by lactic acid bacteria, yeast, and acetic acid bacteria, has gained popularity globally. Fermented beverages like kombucha are believed to offer more health benefits compared to their unfermented counterparts due to the direct action of microbes and their metabolites. They are also a source of bioactive peptides linked to various beneficial activities related to endocrine, cardiovascular, immune, digestive, and neuro-system functioning. Additionally, their low pH, resulting from the presence of various acids, aids in overall health. Glucuronic acid in kombucha improves detoxification and has antimicrobial effects (Marsh *et al.* 2014). In study, Canovas *et al.* (2023) introduced a novel fermented beverage, similar to kombucha, enriched with broccoli by-products. These by-products, rich in organosulfur compounds, underwent biotransformation, resulting in metabolites that were more bioaccessible, bioavailable, and bioactive. The newly developed beverages exhibited variations in physicochemical parameters such as pH, acidity, and °Brix. Phytochemical characterization revealed diverse levels of metabolization of glucosinolates, transforming into isothiocyanates during the plant material infusion. These findings underscore the potential for increased concentrations of bioactive compounds to enhance bioavailability and confer health benefits, particularly in terms of anti-inflammatory activity. Providing further evidence of augmented biological advantages holds promise for advancing the development of innovative functional beverages.

Jablonska *et al.* (2023) aimed to identify the optimal yeast starter culture for producing low-alcohol fermented beverages using Kombucha, renowned for its taste and health benefits. Through meticulous analysis, which included pH levels, alcohol content, microbiological aspects, antioxidant capacity, overall phenolic content and sensory evaluation, they determined that the quality of these beverages significantly depended on the chosen yeast starter cultures. The resulting low-alcohol drinks exhibited favorable characteristics, such as reduced alcohol content, elevated antioxidant levels, and satisfactory microbiological and sensory profiles. These discoveries offer an encouraging basis for further investigation into the potential of fermented Kombucha tea in the development of low-alcohol beverages.

Miscellaneous beverages

The realm of non-carbonated herbal beverages, commonly referred to as "miscellaneous beverages," is experiencing a robust surge in both availability and market demand. These beverages encompass a wide variety of non-alcoholic drinks prepared through non-traditional methods, with ready-to-drink and energy drinks being prominent examples. Common ingredients include melissa, ginseng, guarana, kava root, and gingko biloba. These beverages are marketed with claims emphasizing lifestyle values such as vigor, stimulation, relaxation, tranquility, and disease-fighting abilities (Gruenwald, 2009). Table 3 depicts various miscellaneous beverages with their *in-vivo* and human study validated medical potencies.

One such product already on the market is Haelan, a fermented soy supplement made by Haelan 951 Products Inc. based in Seattle, USA. It is highly nutritive and serves as a safe nutrient adjunct in prostate cancer treatment, with several in-vivo and human trials demonstrating significant positive effects in chemopreventing tumor regression (Nair and Fams, 2004). Another product, Mr. Pink, is a Ginseng-based energy drink containing 1000mg Ginseng along with other vitamins. *In-vivo* trials of ginseng extracts have shown efficacy against influenza virus, malaria, cancer, and osteoporosis (Yoo *et al.* 2012; Han *et al.* 2011; Yun and Choi, 1990; Seo and Kim, 2011). A fermented drink from Korean ginseng and mushroom mycelium has also demonstrated immune-stimulating properties (Park *et al.* 2009).

Table 3: Validated medical potencies of miscellaneous beverages

Beverage	**Country**	**Disease controlled**	**Reference**
Haelan951®	Woodinville, WA, U.S.A.	Cancer	Nair & Hernandez 2002; Nair & Fams, 2004
FFD-410 (HiOwna-Jr.)	Bangalore, India	Immunostimulant, antioxidant, cognition improvement	Anturlikar *et al.* 2013
Ginseng beverage	India	Immnostimulation	Park *et al.* 2009
Tart jerry beverage	Geneva, NY, USA	Insomnia	Pigeon *et al.* 2010
Foeniculum vulgare and *Cymbopogon proximus* beverage	Giza, Egypt	Calcium oxalate renal crystal formation	Ibrahim & El-Khateeb, 2013
Radix astragali	China	Cyclophosphamide induced immunosuppression	Liu *et al.* 2013
Green tea, grape seed, grape peel, shiitake mushroom beverage	Norwich, UK	Common-cold	Schutz *et al.* 2010
Chamomile, meadowsweet, and willow bark	Dublin, Ireland	Inflammation	Drummond *et al.* 2013
Cranberry extracts	Italy	Urinary tract infections, cardiovascular and gastroenteric diseases	Colletti *et al.* 2021
Kefir	Eastern Europe, Russia	Anti-inflammatory effects, reduced cardiac hypertrophy, and reduced kidney hypertrophy	Farag *et al.* 2020; Guzel-Seydim *et al.* 2021; Dahiya and Nigam, 2023
Milk Kefir	Eastern Europe, Russia	Milk Kefir consumption reduced erythrocyte sedimentation rate and C-reactive protein levels in Crohn's disease patients while increasing hemoglobin levels.	Ozcan *et al.* 2019

The popularity of such drinks is increasing due to the scientific validation of the claims made by producers. FFD-410 (HiOwna-Jr.), a herbal drink manufactured by Himalaya Drug Company, India, has proven to be an immune stimulant, antioxidant, and cognition enhancer in rats, composed of herbal extracts from *Eleusine coracana, Emblica officinalis, Colostrum* sp, *Centella asiatica,* and *Piper nigrum* (Anturlikar *et al.* 2013).

A randomized, double-blind, cross-over trial conducted by Pigeon and co-workers in 2010 demonstrated the positive effect of Tart Cherry beverage on adults with insomnia, attributed to the presence of melatonin and anti-inflammatory agents. Additionally, Ibrahim and El-Khateeb (2013) developed a herbal beverage from *Foeniculum vulgare* and *Cymbopogon proximus* for inhibiting or preventing calcium oxalate crystals formation, both found to inhibit kidney stone formation. The use of *T. wallichiana* (Himalayan yew) bark for beverages and medications has historical significance, with paclitaxel, a chemical found in yew bark, becoming a powerful anticancer pharmaceutical under the brand name TAXOL.

Similarly, the historical uses of mayapple roots led to the invention of the podophyllin class of anticancer medicines (McGovern *et al.* 2010). The diverse biological effects of Honokiol, one of the bioactive elements of *Magnolia officinalis,* have sparked significant research interest. A composite herbal beverage from *Radix astragali* and other herbs showed immune-boosting properties in mice (Liu *et al.* 2013). Honeysuckle, a commonly utilized Chinese herb, has been discovered to suppress the Influenza virus, effectively tackling a significant threat to public health (Zhou *et al.* 2015).

Kefir, a fermented dairy beverage, provides numerous health benefits such as enhanced digestion and regulation of the gut microbiome. It has been consumed for millennia and is considered a functional food (Farag *et al.* 2020; Guzel-Seydim *et al.* 2021; Terpo and Mantzourani, 2019). Kefir stands as a fermented dairy drink that sets itself apart in both texture and flavor when compared to the well-loved yogurt. In contrast to yogurt, which relies on lactic acid bacteria for fermentation, kefir's production involves the use of kefir grains as a pre-culture. This unique approach involves the interaction of various bacteria and yeast strains within the kefir grains, leading to the distinct probiotic attributes found in kefir (Dahiya and Nigam, 2023). Kefir originates from the northern slopes of the Caucasus Mountains and is believed to be at least 1000 years old. Numerous studies have proposed that regular consumption of kefir offers various health advantages. These include enhanced digestion, increased lactose tolerance, antioxidant properties, antibacterial effects, modulation of the gut microbiome, regulation of plasma glucose levels, mitigation of obesity-related effects, improvement of cholesterol levels, anti-inflammatory effects, reduction of cardiac hypertrophy, alleviation of kidney hypertrophy, and anti-mutagenic effects (Farag *et al.* 2020; Guzel-Seydim *et al.* 2021; Dahiya and Nigam, 2023).

Some studies have explored the development of herbal beverages using ingredients like kidney beans and chickpeas, highlighting their antioxidant and anti-inflammatory actions (Chen *et al.* 2019; Aguilar-Raymundo and Vélez-Ruiz, 2019). Glenn-Davi *et al.* (2022) evaluated the effects of fermentation on the anti-inflammatory and anti-platelet properties of both homemade and commercially purchased bovine dairy and almond, coconut, and rice-based dairy alternatives. Fermentation enhanced the functional properties of these beverages, ultimately improving their anti-inflammatory and anti-platelet properties. The proliferation of non-carbonated herbal drink can be attributed to different parameters such as lactose intolerance, milk allergies, and the increasing embrace of vegetarian diets. The surge in interest and market demand for these beverages arises from the convergence of traditional empirical wisdom with contemporary scientific substantiation, offering consumers a comprehensive spectrum of choices that cater to both sensory preferences and health-conscious orientations.

Gaps and challenges in the area and their possible solutions

Non-conventional beverages represent a fascinating intersection of food science, biotechnology, and health. This area encompasses innovative beverages that go beyond traditional refreshment to offer biotherapeutic benefits. These benefits may encompass a variety of aspects ranging from immune modulation and gut health improvement to the mitigation of chronic diseases. However, despite the potential, there are certain gaps and challenges in this field which are discussed hereafter, along with potential solutions.

GAPS AND CHALLENGES

Regulatory challenges

One significant challenge in this field is the intricate regulatory environment. Non-conventional beverages with biotherapeutic properties may not align easily with existing food or drug classifications. Identifying suitable regulatory pathways for these products can be perplexing, time-consuming, and costly.

Safety and efficacy

The development of biotherapeutic beverages necessitates thorough testing to guarantee their safety and effectiveness. Conducting clinical trials for beverages presents distinct challenges owing to the fluid nature of the product and the requirement to establish consistent dosing and bioavailability.

Consumer perception

Convincing consumers about the efficacy and safety of these biotherapeutic beverages can be challenging. There might be skepticism or lack of understanding about their mode of action and benefits.

Formulation stability

Maintaining the bioactivity of therapeutic compounds in a beverage format can be tricky. Factors like processing, storage conditions, and interaction with other ingredients can impact the stability and efficacy of the biotherapeutic components.

POSSIBLE SOLUTIONS

Collaboration and regulation

Collaboration between researchers, food scientists, and regulatory bodies is essential. Creating a streamlined regulatory framework that accommodates the unique nature of biotherapeutic beverages can encourage innovation while ensuring safety and compliance.

Advanced testing methods

Creating innovative testing methodologies can aid in evaluating the safety and effectiveness of biotherapeutic beverages more effectively. This could entail utilizing in vitro models, advanced analytical techniques, and predictive modeling to streamline the testing process.

Ingredient compatibility studies

In-depth research into ingredient interactions and formulation stability is crucial. This could involve studying how different compounds in the beverage matrix interact over time and under various conditions, leading to more stable and effective products.

Personalized nutrition

Tailoring biotherapeutic beverages to individual needs through personalized nutrition could enhance their efficacy. Utilizing data from genetics, gut microbiota, and other health indicators could help formulate beverages that are more targeted and effective.

Long-term studies

Conducting long-term studies to track the effects of biotherapeutic beverages on various health parameters can provide a more comprehensive understanding of their benefits and potential drawbacks.

Partnerships with healthcare providers

Collaborating with healthcare professionals can lend credibility to biotherapeutic beverages. Healthcare providers can recommend these beverages as part of holistic treatment plans, further integrating them into the healthcare ecosystem.

To summarize, the field of non-conventional beverages as emerging biotherapeutics holds significant promise, but it's not without its challenges. By addressing regulatory complexities, ensuring safety and efficacy, educating consumers, and advancing scientific methods, these gaps can be bridged, leading to the creation of effective and widely accepted biotherapeutic beverages that contribute to human health and well-being.

CONCLUSION

Non-traditional beverages encompassing a range of categories, such as alcoholic, herbal, teas, and miscellaneous beverages, have gained prominence across diverse global regions due to their inherent functional properties conducive to health enhancement. The progressive evolution of their manufacturing processes underscores the exigency for rigorous scientific scrutiny aimed at substantiating the therapeutic potentials attributed to these beverages. While a modest fraction of these beverages have undergone experimental validation using animal models, a substantially smaller percentage has been subjected to clinical trials. The discerned potential of these evaluated beverages in clinical contexts, particularly concerning prevalent health ailments encompassing cancer, cardiovascular disorders, diabetes, and oxidative stress, is indeed noteworthy. In light of the remarkable attributes exhibited by these non-conventional beverages, a comprehensive regimen of scientific validation coupled with impactful marketing is strongly advocated. This approach is essential not only to comprehensively comprehend the intricate attributes of these bottled offerings bestowed by nature but also to foster their wider recognition and adoption.

The emergence of non-conventional beverages as biotherapeutics represents a paradigm shift in the beverage landscape. It amalgamates scientific exploration, formulation innovation, regulatory coherence, and consumer preferences to redefine the potential of beverages beyond conventional paradigms. The journey towards realizing the full scope of non-conventional beverages as emerging biotherapeutics necessitates overcoming challenges through innovative solutions and collaborative endeavors. As this emerging field continues to develop, it holds the potential to improve global health and well-being by merging science, technology, and culinary enjoyment.

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