Clinically relevant materials & applications inspired by food technologies

Xi Cui,[a,b,c] Kuan Rei Ng,[c] Kong Fei Chai,[c] and Wei Ning Chen[c,d]*

[a]Interdisciplinary Graduate School, Nanyang Technological University, 50 Nanyang Avenue, 639798, Singapore
[b]Advanced Environmental Biotechnology Centre, Nanyang Environment & Water Research Institute, Nanyang Technological University, 1 CleanTech Loop, CleanTech One, No. 06-08, 637141, Singapore
[c]Food Science and Technology Programme, Nanyang Technological University, 62 Nanyang Drive, 637459, Singapore
[d]School of Chemical and Biomedical Engineering, Nanyang Technological University, 62 Nanyang Drive, 637459, Singapore

Summary

Food science and technology have a fundamental and considerable overlap with medicine, and many clinically important applications were borne out of translational food science research. Globally, the food industry - through various food processing technologies - generates huge quantities of agro-waste and food processing byproducts that retain a significant biochemical potential for upcycling into important medical applications. This review explores some distinct clinical applications that are fabricable from food-based biopolymers and substances, often originating from food manufacturing side streams. These include antibacterial wound dressings and tissue scaffolding from the biopolymers cellulose and chitosan and antimicrobial food phytochemicals for combating antibiotic-resistant nosocomial infections. Furthermore, fermentation is discussed as the epitome of a translational food technology that unlocks further therapeutic value from recalcitrant food-based substrates and enables sustainable large-scale production of high-value pharmaceuticals, including novel fermented food-derived bioactive peptides (BPs).

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Introduction

The term "food science & technology" refers to a huge multidisciplinary umbrella spanning the basic sciences and engineering fields and their interfaces with human food and all aspects thereof. As food sustains all forms of life, fundamental overlap exists between food science and medicine. In addition to the universally acknowledged concept of "food as medicine" (termed "yaoshitongyuan" in traditional Chinese medicine), there are many other diverse facets of food science and technology that are also highly translatable to clinical applications. "Clinical application" refers to research that is directly applied to patient medical testing and/or treatments. The global food industry juggernaut – valued at USD 11 trillion in 2019 and growing rapidly – generates both agro-waste (from crop agriculture) and food processing side-streams (from food manufacturing) at enormous scale daily.[1,2] The in principle high biocompatibility of food-derived substances and matrices, combined with their superior homogeneity over public food waste, makes these food production side-streams highly convenient and reliable bioresources - Still ripe with biochemical riches and strong potential for valorisation and upcycling into impactful biomedical and clinical applications. Notable examples of such food side streams include sugarcane bagasse, coffee grounds, soybean okara and brewers' spent grain. Unfortunately, valorisation and upcycling of these food side streams are not yet common practice, with most food-related businesses simply opting for pure disposal.

In this review, we expand on various distinct impactful clinical applications derivable from or inspired by food-based bioresources and food science & technology approaches (**Figure. 1**). Of particular interest are solutions borne out of food waste valorisation approaches towards the twin goals of reducing global food waste and the global carbon footprint. Fermentation is the quintessential translational food technology that connects these discussed facets by unlocking further value from recalcitrant food waste substrates and enabling sustainable large-scale production of high-value naturally scarce pharmaceuticals via sophisticated biotechnological schemes (Tables 1–3).

Food processing side streams refer to byproducts originating from any stage of a food manufacturing process via various food technologies. These side streams are generated in huge volumes daily by the global food

*Corresponding author at: Food Science and Technology Programme, Nanyang Technological University, 62 Nanyang Drive, 637459, Singapore.
E-mail address: wnchen@ntu.edu.sg (W.N. Chen).

Figure. 1. Summary of biomedical applications that can be derived from food technologies.

Biomaterials	Clinical Application	Refs.
Cellulose	Wound dressing (hydrogel), antimicrobial, anti-freezing, non-drying properties	4
	Wound dressing (film), exudate absorption, controlled drug release	5
	Tissue engineering, skin and bone	16
	Sensor for personal health care monitoring (paper)	29
	Biosensor (hydrogel)	30
	Tissue engineering, bone	15
	Drug delivery	23
Cellulose nanofibril	Wound dressing, Antimicrobial property and mode of action	6
Nanocrystalline cellulose	Wound dressing, Antimicrobial property	7
Chitosan	Wound dressing, Antimicrobial property	8
	Wound dressing, Antimicrobial property	9
	Wound dressing (hydrogel), Haemostatic	12
	Surgical suture	13
	Surgical suture, improved colonic anastomosis	14
	Tissue engineering (hydrogel), kidney-specific	17
	Drug delivery, kidney-specific	25
	Drug delivery, antimicrobial, rechargeable	26
	Hypocholesterolaemic	31
	Haemostasis	10
	Antimicrobial against multi-drug resistant bacteria	32
	Tissue engineering (hydrogel), bone	18
β-chitosan	Drug delivery, targeted	27
Alginate	Tissue engineering (hydrogel)	19
	Tissue engineering for vascular medicine	20
	Tissue engineering, bone	21
Oxidized alginate	Drug delivery, transdermal	28
Collagen	Drug delivery (hydrogel), controlled release	24
Fibrin		
Gelatine		
Nano carboxymethyl cellulose-alginate/chitosan		

***Table 1*: Food-derived biopolymers and their clinical applications, sorted by biopolymer type.**

Food Source	Compound	Clinical Application	Antimicrobial Activity Against	Refs.
Ashitaba *(Angelica keiskei)*	Isobavachalcone	Antibiotic lead	MRSA, VRE	58
Mangosteen *(Garcinia mangostana)*	α-mangostin	Antibiotic lead		
Tea *(Camellia sinensis)*	Complex Extract	Adjuvant to Nalidixic acid	MDR *Salmonella typhi*	42
English walnut *(Juglans regia)*	Complex Extract	Adjuvant to Oxacillin	MRSA	
Coffee *(Coffea spp.)*	Caffeine	Adjuvant to Gentamicin	*Staphylococcus aureus* (clinical isolate)	47
Various food crops & herbs	Verbascoside	Adjuvant to Gentamicin	*S. aureus* (clinical isolate), MRSA, *Escherichia coli* (clinical isolate)	
Lemon verbena (*Lippia citriodora*)	Complex Extract	Adjuvant to Gentamicin	*S. aureus (clinical isolate)* *E. coli* (clinical isolate)	
Pomegranate *(Punica granatum)*	Complex Extract	Adjuvant to Novobiocin	*Acinetobacter baumannii*	59
Lemongrass *(Cymbopogon citratus)*	Essential oil	Adjuvant to Chloramphenicol	*Enterobacter aerogenes* EA27, *E. coli* AG102	49
Chlorophyll-containing foods	Phytol	Surface disinfectant	*E. coli, Candida albicans, Aspergillus niger*	52
Oregano (*Origanum vulgare*), cinnamon (*Cinnamomum sp.*), clove (*Syzygium aromaticum*)	Essential oil mixture	Surface disinfectant	*E. coli,* mesophilic aerobic bacteria, yeasts & moulds	53
Marjoram *(Origanum majorana)*	Essential oil	Surface disinfectant	*E. coli, Listeria monocytogenes*	54
Thyme *(Thymus vulgaris)*	Essential oil	Surface disinfectant	*E. coli, Listeria monocytogenes*	

***Table 2*: Plant food-derived antimicrobials, their specific activity and potential clinical applications.**

Source	Product	Bioactive peptides	Bioactivities	Refs.
Cow's milk	Cultured milk	P1: QYVLSRYPSYGIN P2: KYIPIQYVLS P3: INNQFLPYPYYAKPA P4: DKTEIPTINTIASGEPT P5: AVRSPAQILQWQ P6: VIESPPEINTVQ P7: NTVPAKSCQAQPTTm P8: NVPGEIVESL P9: VYPFPGPIPN P10: HKEMPFPKYPVEPFTESQ P11: SQSKVLPVPQKAVPYPQ P12: SWMHQPHQPLPPT P13: VVPPFLQPE P14: EDELQDKIHPF P15: FPKYPVEPF P16: APSFSDIPNPIGSENSE P17: KHQGLPQEVLNENLL P18: PFPEVFGKE P19: QGPIVLNPWDQVKR P20: ALPQYLKTVYQHQK P21: IQPKTKVIPYVRYL	Antibacterial (P4, P6 and P20-P22), immuno-modulating (P8 and P17) and ACE-I (P9)	70

Table 3 *(Continued)*

Source	Product	Bioactive peptides	Bioactivities	Refs.
		P22: FLKKISQRYQKF		
		P23: EKDDTGTPITKIELVPSH		
	Prato cheese	P1: αS1-CN(f1-9) (m/z 1141)	Antihypertensive (P1 and P3) and	71
		P2: β-CN(f194-209) (m/z 1718)	ACE-I (P1 and P2)	
		P3: β -CN(f193-206) (m/z 1556)		
	Fermented milk	P1: VPP	ACE-I	66
		P2: IPP		
		P3: LKP		
		P4: ALPM		
		P5: PGPIHD		
		P6: VAGTWY		
		P7: DN		
		P8: IPI		
	Yoghurt	GABA	Antihypertensive, antidiabetic and antiproliferative	65
		P1: YQEPVLGPVRGPFPIIV	Antioxidant and antiproliferative	67
		P2: SLPQNIPPLTQTPVVVPPF		
Pork	Pork protein extract	P1: MDLR	Antioxidant	72
		P2: PYLR		
		P3: FDLR		
		P4: EAAPYLRK		
		P5: EAAPYLR		
		P6: AAPYLR		
		P7: KALLS		
		P8: VLAR		
		P9: LPLK		
		P10: AKLPA		
		P11: VNGFGR		
		P12: KLPA		
		P13: YGRAL		
		P14: VVFK		
		P15: APARKF		
		P16: KPVSPL		
		P17: THLDT		
		P18: FLSNH		
		P19: VKVG		
		P20: AAKLPA		
		P21: KLAAP		
		P22: KPVSPLL		
		P23: LLVFH		
		P24: KPVSPLLL		
		P25: VLLFH		
Ruditapes philippinarum clam	-	P1: VISDEDGVTH	ACE-I	73
		P2: LDSGDGVTH		
		P3: VVVGDGAVGK		
		P4: FAGDDAPRA		
Soybean	Natto	P1: KFNKYGR	Angiogenic (P1-P5 and P7) and lipopolysaccharide-neutralizing (P1-P7) activities	74
		P2: FPFPRPPHQK		
		P3: GQSSRPQDRHQK		
		P4: QRFDQRSPQ		
		P5: ERQFPFPRPPHQK		
		P6: GEIPRPRPRPQHPE		
		P7: EQPRPIPFPRPQPR		
Chicken feather	-	P1: LPGPILSSFPQ	Antioxidant	75

***Table 3*: Selected peptides with bioactivities obtained from various food sources via microbial fermentation.**

industry. Valuable raw materials (green) are extracted from these side streams and then converted into impactful clinical applications (blue). Fermentation (red) is a pivotal translational food technology for the value-added transformation of these recalcitrant materials into such applications.

Biocompatible food-based biopolymers derived via food processing technology for clinical biomaterial applications

In medical and clinical sciences parlance, "biomaterial" refers to any polymer or substance that has been engineered to interact with biological tissues or systems for therapeutic or diagnostic purposes, while "biocompatibility" refers to said material's propensity to elicit undesirable immunological or toxic responses from the patient. Clinical applications necessitate biomaterials to be biocompatible as well as certified medical grade to minimize immune rejection and infection risks, respectively - particularly important in invasive surgical implementation cases. For clinical biomaterial applications, natural biopolymers have some inherent advantages over synthetic petroleum-based or inorganic biomaterials (glass, ceramic, metals), such as overall higher biocompatibility. Food in all forms consists of some combination of all of the different existing biopolymers (carbohydrates, proteins and polynucleotides) and is by definition highly biocompatible and therefore a robust fit for almost all clinical biomaterial applications. The polysaccharides cellulose and chitosan tend to dominate, followed by fibrous protein-derived polypeptides such as collagen and gelatine. Cellulose is the most abundant biopolymer in nature, consisting of a linear chain of β (1→4)-linked D-glucose units. The omnipresence of cellulose in food makes it both highly viable and economical as a substitute for petrochemical-derived plastic polymers, particularly in wound care applications such as dressings and sutures. Chitin, the second most abundant biopolymer on Earth, is another similarly linear polysaccharide built from β-1,4-linked N-acetylglucosamine units and a principal component of the exolayers and exotissues of insects, fungi, invertebrates and fish. Chitin can be further deacetylated via chemical or enzymatic means to yield chitosan, the true biopolymer of interest, especially for wound care. Unique chemical and biological properties are liberated by the deacetylation of the chitin backbone monomers, which vastly improves aqueous solubility and antimicrobial activity as a result of the exposed amino moieties on the glucosamine monomer subunits. Plant crop and seafood processing side streams are hugely underutilized and highly sustainable sources of cellulose and chitosan, respectively, which are usually extracted via energetic hydrolysis-based approaches to be fabricated into wound care, tissue scaffolding or drug delivery applications, expanded on below.

Wound dressings

Wound dressings are widely used in clinical settings - especially postsurgery - to avoid secondary injury, minimize infection risk and accelerate wound healing and recovery. Presently, synthetic polymers are the market default in wound care due to cost and abundance. The primary weaknesses of synthetic polymer-based wound dressings — low biocompatibility and biodegradability — nevertheless remain. In terms of biocompatible substitutes, hogskin[3] or human skin grafts were discovered very early to be effective at protecting deeper skin tissue layers from further physical damage and infection while also retaining strong water permeability. However, due to their high cost and perishability, such natural skin grafts were quickly determined to be clinically impractical. Cellulose is a strong substitute candidate due to its superior biocompatibility, biodegradability, sustainability and low solubility in common organic solvents. Cellulose derived from valorisation of Durian husk was successfully used to fabricate hydrogel wound dressings with both anti-freezing and antimicrobial properties (**Figure. 2**).[4] Cellulose has also been combined with chitosan and alginate — all food-grade biopolymers - to form a highly biocompatible biomaterial composite applied as a direct wound dressing that was found to be capable of both wound exudate absorption and controlled release of topical medications.[5] Chitosan, with its inherent antimicrobial property, is theoretically superior to cellulose for wound care applications.[6,7] Chitosan has been combined with polyvinyl alcohol and copper to successfully demonstrate antimicrobial activity against both gram-positive and gram-negative bacteria.[8] In another work, chitosan was incorporated with clove and melaleuca essential oils to form an antimicrobial film for wound dressing.[9] Haemostatic potential — a particularly desirable quality for wound dressings - of chitosan was also observed in studies[10,11] with a chitosan/cyclodextrin hybrid hydrogel reportedly exhibiting a good haemostatic effect by decreasing the blood loss and shortening haemostasis times.[12]

Surgical sutures

Another important aspect of wound care in clinical settings is that sutures are typically used in invasive surgery to seal deeper surgical incision wounds to facilitate postoperative healing and recovery of the patient. Similar to wound dressings, while modern sutures are mostly synthetic and petroleum-based, biocompatibility, biodegradability and antimicrobial effects remain desirable properties for surgical sutures, particularly since sutures are commonly not physically removed but left to safely biodegrade within the patient. Cellulose filaments accordingly show promise as sutures and artificial vasculature in microsurgery procedures, wherein oxidized regenerated cellulose can prevent haemorrhage, a serious medical complication. Additionally,

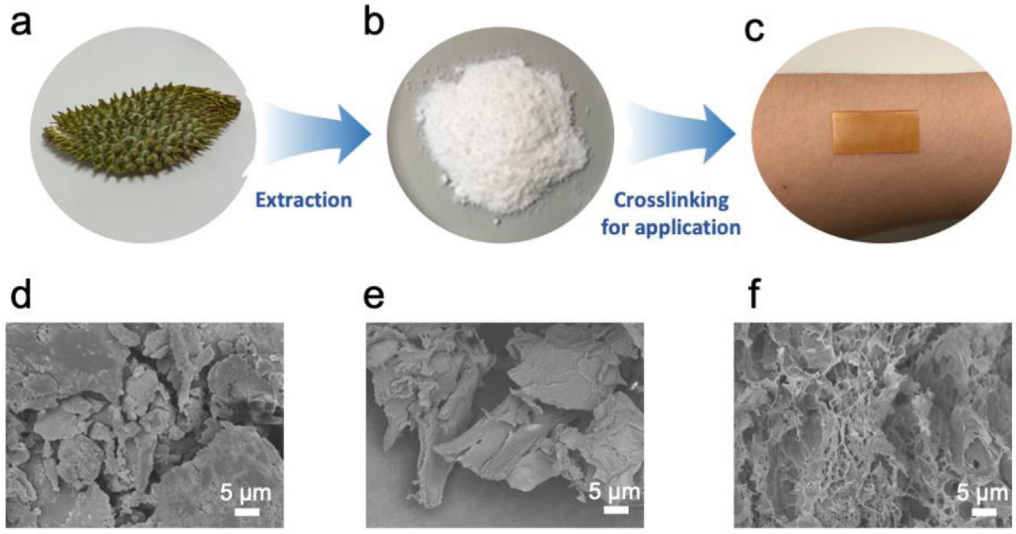

Figure. 2. Clinical applications of biocompatible materials derived from food processing side streams. Cellulose is first extracted from cellulosic food wastes, e.g., (a) Durian husk, and then made into (c) cellulose hydrogel through (b) extracted cellulose. (d), (e), and (f) are SEM images of dried Durian husk powder, Durian husk cellulose, and fracture surface of Durian husk cellulose hydrogels, respectively.

chitosan's similarly strong potential here was demonstrated via enhanced antimicrobial, mechanical, and frictional properties when it was coated on the surface of synthetic nylon sutures.[13] In another work, chitosan-coated surgical sutures were applied in colonic anastomosis, showing improved adhesion and reinforcement both *in vitro* and *in vivo*.[14]

Tissue engineering

Tissue engineering is a highly interdisciplinary clinical subfield that involves tissue or whole organ regeneration/replacement from specific cellular growth — often on tissue scaffolds — as a therapeutic approach. Biocompatibility and biodegradability are once again important prerequisites. Cellulose expectedly shows strong potential as a tissue scaffolding material in tissue transplantation as well as bone and skin tissue engineering.[15,16] Thermosensitive chitosan hydrogel was also used as an injectable scaffold to deliver mesenchymal stem cells to targeted sites for the treatment of acute kidney injury, resulting in the amelioration of renal function and tubular cell proliferation.[17] Alginate, another less common food polysaccharide polymer derived from edible brown seaweed, has unique clinical potential owing to its anionic and gelling properties when combined with divalent cations, e.g., $Ca^{2+,}$ and has seen applications in tissue engineering as well.[18,19] For nonpolysaccharide-based biopolymers, collagen, an extracellular matrix protein and the most abundant protein in mammals present as connective tissue in tendon, ligament, and skin, is an obvious candidate as a scaffolding biomaterial,[20] while fibrin, another protein derived from meat wastes, also seems to be useful.[21] In one highly innovative study, stale bread — typically an undefined solid matrix of carbohydrates and proteins — was utilized as raw material for bioactive scaffolds.[22]

Drug delivery

Drug delivery involves the transport of pharmaceutical compounds to target tissue(s) and/or organs, usually involving drug carriers that control their rate of release and absorption into the target tissue to achieve a desired therapeutic effect at the appropriate dose. Food biopolymers are all naturally excellent fits as drug carriers and have been trialed extensively via myriad formulations. Nanocrystalline cellulose[23] and modified carboxymethyl cellulose[24] have been used in drug delivery systems, either on their own or in composites with other biopolymers. Low molecular-weight chitosan can be used to fabricate tissue-directed drug delivery nanocomplexes for renal fibrosis treatment, and its unique renal tissue-specific property is attributable to the presence of primary amines on the backbone glucosamine units.[25] Methacrylic acid-modified polyurethane was also combined with antimicrobial chitosan to ensure aseptic drug delivery.[26] Alginate nanoparticles[27] and gelatine[28] have seen similar drug delivery applications.

Other clinical applications of food-based biopolymers

Cellulose has shown strong potential as a biosensor implant material. $NiSe_2$-modified cellulose was used to fabricate a biosensor cum personal health care monitor,[29] and okara-derived cellulose was fabricated into hydrogels for human movement detection as a biosensor.[30] A hypocholesterolaemic effect of chitosan in humans was also observed before lowering the serum low-density lipoprotein (LDL) cholesterol

concentrations,[31] which makes it an attractive alternative biomaterial for cardiovascular stent design. β-Chitosan, a rarer form of chitosan extracted from molluscs as opposed to α-chitosan from crustaceans, has demonstrated antimicrobial effects against multidrug-resistant bacteria, a serious problem in nosocomial settings.[32] In general, infection remains a critical recurrent problem in most clinical wound care and biomaterial-related applications, particularly multidrug-resistant pathogens that tend to surface in nosocomial settings.

Natural food antimicrobials to counter antibiotic resistance and nosocomial infections

Antibiotic resistance in pathogens has become a major global public health problem. Continual misuse of antibiotics in humans and livestock has created multiple multidrug resistant (MDR) pathogenic strains, against which modern medicine is running out of treatment options.[33] MDR-associated nosocomial or hospital-acquired infections are of particular concern due to significantly increased patient mortality risk.[34,35] The strains of high concern are carbapenem-resistant *Acinetobacter baumannii, Pseudomonas aeruginosa* and *Enterobacteriaceae,*[36] Antibiotic resistance in pathogens can arise through numerous mutations via many different possible microbial mechanisms: biofilm formation, altered enzyme or ligand binding site affinities, efflux pumps, deactivating enzymes, e.g., beta-lactamases, etc.[37,38] Natural food antimicrobials — the majority of which are plant-derived antimicrobial phytochemicals — represent potent novel leads against MDR pathogens via the following applications: antibiotic therapy, surface disinfectants or sanitizers and enhancement of personal protective equipment (PPE) in clinical settings. Similar to food-based biopolymers, food production side streams represent rich and readily available bioresources to tap for antimicrobial phytochemicals of interest.

Antimicrobial phytochemicals for antibiotic therapy

Plant natural compounds or phytochemicals remain a precious yet largely untapped resource in the war against MDR pathogens, with antibiotics mostly of microbial or synthetic origin, rather than botanical origin, employed today.[39] Plant secondary metabolites are divided into classes such as terpenoids, alkaloids, organosulfur compounds and phenolics and are often relatively small molecules (lower Mr range < 500) in comparison to other classes of active lead compounds, e.g., peptides and biologics. For the screening of plant materials for antibiotic drug discovery, there remains significant room to explore using ethnopharmacological, computational and sometimes serendipitous approaches.[40,41] Phytochemicals may be utilized in antimicrobial applications as either highly purified lead compounds or botanical extracts, which are complex mixtures of plant essential oils (EOs). The antimicrobial potential of myriad dietary phytochemicals has been widely reported in the literature[42] based on different mechanisms depending on molecular structure: efflux pump inhibitory activity, protein alkylation, different enzyme inhibition and bacterial membrane disruption.[43] It has also been proposed and observed that synergism between phytochemical components of a complex botanical extract may result in improved antimicrobial effects over single purified phytochemicals. With regard to clinical antibiotic therapy, phytochemicals have already proven their therapeutic value when coadministered with traditional antibiotics as adjuvants.[44,45] For example, isobavachalcone and a-mangostin, both plant-derived flavonoids that abolish colistin resistance by some gram-negative bacteria, were also found to exhibit potent antibacterial activities against vancomycin-resistant *Enterococcus faecium* (VRE).[46] Coadministration of gentamicin with any of the following food-based materials - *Aloysia citrodora* extract, its active lead compound verbascoside, or caffeine - improved antibacterial activity against drug-resistant *Staphylococcus aureus* and *Escherichia coli* strains obtained from clinical isolates, when none of these adjuvants were effective.[47] An extract from pomegranate (*Punica granatum)* was able to enhance the antibacterial activity of novobiocin against *Acinetobacter baumannii*, an important nosocomial pathogen with inherent multidrug resistance.[48] Lemongrass (*Cymbopogon citratus)* essential oil (EO), apart from demonstrating significant antibacterial activity on its own, was able to restore bacterial susceptibility to chloramphenicol of certain MDR strains.[49] While many phytochemicals do not match classical antibiotics in terms of pure bactericidal or bacteriostatic activity (MIC or MBC) on a per unit mass basis, dietary phytochemicals confer numerous additional health-promoting benefits in addition to antimicrobial activity. In addition, since a large majority of these natural plant antimicrobials already comprise part of the healthy human diet via their existence in fruits and vegetables, they are generally considered to possess a lower risk of negative side effects, which is one of the primary drawbacks of classical antibiotic therapy.[50] Moreover, botanical antimicrobials are themselves less likely to generate drug resistance, although that could be partly attributed to them being relatively unexplored and thus underutilized.[51] These advantages further highlight the promise of natural food phytochemicals as adjuvants or simply "dietary supplements" in antibiotic therapy, especially against MDR pathogenic strains.

Antimicrobial phytochemicals as disinfectants, sanitizers and enhanced personal protective equipment (PPEs)

The strong translational potential of natural food antimicrobials for clinical applications is not limited to only

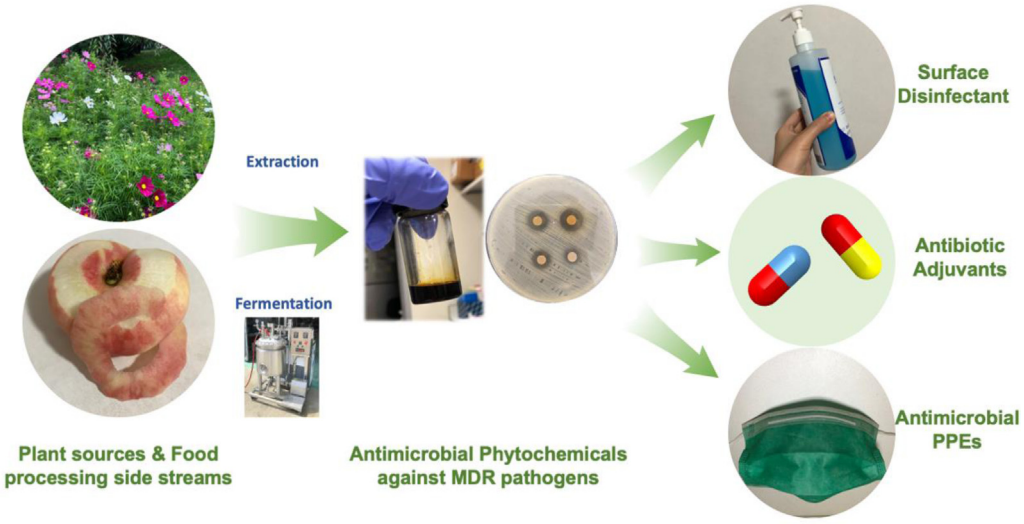

Figure. 3. Antimicrobial phytochemicals for combating multidrug-resistant pathogens in clinical settings. Antimicrobial phytochemicals are derived from natural plant sources or, alternatively, food processing side streams. Via extraction methods that may involve fermentation, antimicrobial botanical extracts or purified lead compounds derived therefrom are then used for antibiotic therapy, disinfectants and sanitizers and infused into PPEs for enhanced protection.

antibiotic therapies but also to surface disinfectants, sanitizers or enhanced personal protective equipment (PPE) via incorporation of antimicrobials into their fabric or material – of particular importance in the present COVID-19 pandemic (Figure. 3). Relevant examples are as follows: Phytol derived from *Leptadenia pyrotecnicais* was trialled and showed promising, dose-dependent disinfectant properties against bacteria, yeast and mould.[52] In another work, a combined oregano-cinnamon-clove essential oil formulation showed a strong reduction in total mesophilic aerobic bacteria and mould-yeast counts on various surfaces as well as air.[53] Another study showed thyme and marjoram EO-based disinfectants to be effective at eliminating *E. coli* and *Listeria monocytogenes* biofilms on polypropylene surfaces, and their effects were equivalent or even superior to industrial sanitizers based on per-acetic acid or sodium hypochlorite.[54]

Plant antimicrobials are typically produced via large-scale extractions (maceration, hydrodistillation, Soxhlet, etc.) of medicinal or food crop biomass – either foraged or cultivated - which creates considerable detrimental environmental impact via deforestation, significant waste generation and a carbon footprint. Agricultural crop byproducts and food processing side streams are typically phytochemical rich and are highly economical yet environmentally friendly alternative sources of such compounds.[55] These waste streams may be more ideal sources because they typically consist of fibrous, human-indigestible and inedible plant matter, e.g., seed husks, spent grain, and other lignocellulosic biomass, which conversely accumulate higher amounts of active phytochemicals per unit dry mass. In addition to food extraction technologies, fermentation is another key technology increasingly used to sustainably unlock and extract these valuable phytochemicals from such recalcitrant waste biomass. There is a fast-growing body of literature on the antimicrobial activities of food processing and agricultural byproducts, including their upcycling into potential food applications.[56,57] An antimicrobial reusable face mask was recently commercialized in Singapore, wherein the active antimicrobial component in the mask fabric was derived from industrial nut processing waste (https://www.straitstimes.com/singapore/ntu-scientists-use-antimicrobial-extract-from-seeds-in-reusable-masks). This represents a tangible result of translational research between food science and medicine that is also highly environmentally sustainable and a keynote example in this review.

Fermentation as a pivotal food technology for unlocking pharmaceuticals and good health

In food science and biotechnology, fermentation refers to the chemical transformation of organic material from and for food purposes via utilization of microbial metabolism. Fermentation typically results in radically altered final products that are nevertheless desirable due to certain compositional and organoleptic profile changes. Despite being a millennia-old practice and one of the oldest food technologies in existence, fermentation is far from being solved or perfected. Countless types exist – from ancient undiscovered artisan recipes brewed in remote regions to highly sophisticated and precise biotechnological schemes. The breadth and depth of

fermentation science & technology have expanded immeasurably in the past century and continue apace. Historically, some key breakthroughs in fermentation were closely tied to medicine, in the case of penicillin and insulin, which both represent key milestones of "red" or medicalbiotechnology. The pasteurization process still stands today as the monumental translational research breakthrough between food science and medicine. In the future, the continuing development and maturation of synthetic biology and metabolic engineering subfields further enable precision fermentation approaches for sustainable high-volume production of natural bioactives and pharmaceuticals.[60,61] Herein, we discuss food fermentation-derived bioactive peptides as prospective novel pharmaceuticals that are underexplored and distinct from established, well-characterized biologics such as insulin, polypeptide drugs and vaccines.

Fermentation of biologically active peptides with diverse health benefits

Bioactive peptides (BPs) are specific protein fragments that are initially inactive within the sequence of the parent protein but are then liberated via microbial enzymatic and proteolytic activities during fermentation processes. BPs have shown various physiological functions, such as antihypertensive, antioxidant, antimicrobial, anticancer, anti-inflammatory, opiate-like, hypolipidaemic and hypocholesterolaemic, antithrombotic and mineral binding activities. These potent physiological effects, allied with high target biospecificities, low bioaccumulation potential and allergenicity risks, make BPs highly attractive and promising novel pharmaceutical candidates with a wide spectrum of potential clinical applications.[62] To date, BPs from food-based fermentations are still a largely unexplored arena. The most common BPs reported in the literature are angiotensin-converting enzyme (ACE) inhibitory peptides. ACE inhibitory peptides are of particular interest as COVID-19 drug candidates, in light of the recent ongoing pandemic.[63] The bioactivities exerted by BPs depend on their structural properties, amino acid composition and sequence - usually with 2-20 amino acid residues and of low molecular weight (<6 kDa) - and in particular identity of N- and C-terminal residues.[64]

Fermentation has been used to hydrolyse food proteins to liberate BPs from their parent proteins via the action of proteases synthesized by fermenting organisms. Yeasts, fungi and lactic acid bacteria (LAB) are typical fermentation starter cultures, with LAB preferring over others due to their generally recognized as safe (GRAS) status. Both solid-state and submerged fermentations have been employed on many different food sources to obtain BPs, including milk and dairy products, meat, cereals, pseudocereals and legumes, fish and shellfish, microalgae, and wastes from agri-food processing. Gamma aminobutyric acid (GABA) is a nonprotein amino acid that can be synthesized via microbial fermentation: GABA can decrease blood pressure, reduce stress, prevent diabetes and inhibit cancer cell proliferation. The presence of high levels of GABA in yogurt contributes to its popularity as a functional dairy product that can be conveniently consumed with regularity. A recent study showed that the GABA content in yogurt could be further enhanced via the addition of simple sugars and commercial prebiotics without the need for pyridoxal 5'-phosphate (PLP) cofactor, a critical coenzyme for most LAB strains that is present at low levels for GABA production through α-decarboxylation of glutamate via glutamate decarboxylase,[65] hinting at an alternative and more feasible long-term therapeutic regime or approach for chronic hypertensive patients. The commercially available and widely known fermented milk-based beverages Calpis and Evolus both claim to contain antihypertensive tripeptides Val-Pro-Pro and Ile-Pro-Pro and could thus fit the same purpose.

Aside from exerting physiological functions instantaneously, many peptides have also demonstrated prodrug properties via gut release by enzymatic activity on ingested food containing protein precursors.[66] The multifunctional β-casein-derived peptides Tyr-Gln-Glu-Pro-Val-Leu-Gly-Pro-Val-Arg-Gly-Pro-Phe-Pro-Ile-Ile-Val and Ser-Leu-Pro-Gln-Asn-Ile-Pro-Pro-Leu-Thr-Gln-Thr-Pro-Val-Val-Val-Pro-Pro-Phe reported in a fermented milk study demonstrated that further *in vitro* gastrointestinal digestion increased their antioxidant and antiproliferative activities,[67] while a whey protein hydrolysate produced by Davisco Foods International, USA, contains glycomacropeptides that purportedly possess anticarcinogenic, antimicrobial and antithrombotic activities. By markedly improving overall gut health, these BPs have the potential to be administered as prebiotic therapy for patients with irritable bowel syndrome, which affects approximately 1 in 10 patients in the United States.[68]

Fermentation is a novel approach for the production of a myriad of health-beneficial BPs, requiring a lower cost compared to enzymatic hydrolysis. Additionally, BPs obtained from microbial fermentation can be purified without further hydrolysis.[64] It is envisaged that once the structure and sequence of a specific BP have been elucidated, precision fermentation could be employed — via engineered microbial platform approaches - to produce the target BP more efficiently and sustainably. The combination of rapidly maturing next-generation sequencing, high-throughput screening and multi-omics approaches in tandem with synthetic biology and metabolic engineering tools will enable ever more precise strain selection, design and optimization of high-productivity microbial cell factories for the production of BPs from various protein sources - either animal or plant origin — or even from low- to zero-value food waste substrates via precision fermentation.[69]

Outstanding Questions

Despite the sizeable body of work accomplished in medicine-directed translational food science research, significant challenges and obstacles remain to be overcome. The useful natural biopolymers cellulose and chitosan are locked behind highly recalcitrant waste biomass (lignocellulosic and chitinous, respectively), which typically require harsh physical and/or biochemical treatment approaches, and extraction from these waste bioresources has significant room for improvement in terms of efficiency, purity and process sustainability. Fermentation has the potential to alleviate these problems but remains largely untested. Despite their many advantages, pure cellulose and chitosan still possess some inherent weaknesses, e.g., mechanical strength, water solubility, and shelf life, that render them not an immediate fit for many applications, which therefore necessitates further innovative engineering – such avenues include composite formulation and polymer functionalization. For natural antimicrobials against antibiotic resistance, phytochemicals as adjuvants in antibiotic therapy have demonstrably worked; further research remains in terms of optimizing drug formulations and dosages for clinical application. The current library of identified and characterised plant natural products is vast, but the unidentified space that remains may be at least an order of magnitude larger. Ultimately, upscaling the production of all of these food-derived bioactive will address the key bottleneck: these phytochemicals or combinations thereof are produced naturally in only minute quantities, and despite rapid progress in the related subfields, precision fermentation via synthetic biology and metabolic engineering approaches remain some way from widespread commercial implementation, with money (capex costs), time (custom process design) and public perception ("naturalness") being major stumbling blocks. Continual research efforts into fermentation science doubtless remain necessary to further optimize and streamline the design and implementation of precision fermentation approaches unique to each separate product.

Conclusion

Myriad clinical applications and solutions have been derived from the food science and technology arenas. As an inadvertent yet inevitable consequence of agricultural and food processing technologies and manufacturing, industrial food side streams present obvious opportunities, as valuable bioresources are still rich in cellulose, chitin/chitosan, phytochemicals, (poly)peptides and lipids. Via interdisciplinary approaches and innovative methods borne out of translational food science research, such valuable bioresources could be readily transformed into biocompatible clinical biomaterials, antimicrobials, bioactive peptides and other valuable pharmaceuticals. Fermentation is key to unlocking the vast biochemical and clinical potential of recalcitrant food waste streams. The ability of fermentative microorganisms to catalyse the biotransformation of inedible and discarded nutritious, medicinal and even delicious microorganisms underlines fermentation's tremendous value-add plus potential as a vital pillar of food technology to solve simultaneously the grand challenges faced by humanity today: reducing global food waste, averting climate change and improving public health.

Search strategy and selection criteria

All references in this review were identified by Google Scholar and PubMed engine searches using the following search terms or combinations and variations thereof: "agro waste"; "food waste isvalorisation"; "Natural biopolymers in medicine"; "Cellulose for medical applications"; "Chitosan for medical applications"; "Antimicrobial phytochemicals"; "antibiotic resistance"; "nosocomial infections"; "food fermentation"; "bioactive peptides". All references fell within the timeframe 1965-2021, but the vast majority of cited works were from the past 10 years.

Contributors

All authors conceived the original draft and edited the final manuscript. All authors read and approved the final version of the manuscript.

Declaration of Competing Interest

The authors declare no competing interests.

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