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REVIEW ARTICLES

Development of customized inner beauty products and customized cosmetics apps according to the use of NRF2 through DTC genetic testing after the COVID-19 pandemic

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Abstract

Background: After the coronavirus disease-19 (COVID-19) pandemic, the definition of health continuity, well-being, and well-dying is also evolving.

Objectives: This review is about the utilization of nuclear factor erythroid 2-related factor 2 (NRF2) for customized inner beauty products and customized cosmetics through Direct-To-Consumer (DTC) genetic testing in the non-face-to-face era that is evolving after the global pandemic.

Methods: In May 2021, we proposed a narrative review as a new report and commentary. It was written with reference to keywords such as "Covid DTC Genetic Test," "Covid 4th industrial revolution," "Covid NRF2," and "Antioxidants." This study was performed by searching on PubMed, Google Scholar, Scopus, and ResearchGate. A total of 432 papers were retrieved, of which 40 were successfully included in this study.

Results: With the rapid transition to a non-face-to-face society after COVID-19, the concept of DTC was born, which allows consumers to receive genetic testing directly without visiting a medical institution. Based on the 4th industrial revolution, a convergence medical device is needed to secure the function as an NRF2 regulator of antioxidants in customized inner beauty products and customized cosmetics.

Conclusion: Therefore, let us look at the fact that a fusion medical device based on the 4th industrial revolution has emerged in the global DTC genetic test market, which is still insufficient to summarize important research results. This study is expected to be an important data for the development of antioxidants as NRF2 regulators in customized inner beauty products and customized cosmetics. As mobile use increases in the future, additional research focusing on app development is needed, and various follow-up studies are also needed.

KEYWORDS
4th industrial revolution, antioxidants, COVID-19, customized cosmetics, DTC genetic test, NRF2

1 | INTRODUCTION

Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) has become a global pandemic with unprecedented consequences. These coronaviruses are becoming an increasingly serious situation in our society due to their long incubation period and unpredictable high prevalence. Although effective vaccines are available, the epidemic is uncontrolled due to high mortality and rapid spread.[1] To minimize this risk of infection, additional general preventive and protective measures are needed to isolate and manage secondary or tertiary waves. So far, four vaccines have reported varying efficacy of approximately 62%–95%, and two of them (Pfizer/BioNTech Corp. and Moderna Corp.) are urgently approved for use by the FDA. Additional access and distribution of these vaccines will save many lives in all countries.[2] If we look at the cases of severe acute respiratory syndrome (SARS) in the past, it was the first infectious disease of the 21st century, killing more than 700 people worldwide. Again, no effective anti-SARS vaccine or drug has been found, despite the urgent need for adequate preparation against SARS outbreaks. Therefore, the characterization, familial classification, and kinetic mechanism of SARS coronavirus (SCV) helicase-nsP13 were studied. Potent inhibition of SARS helicase by the native flavonoids, myricetin, and scutellarein has revealed the identification of novel chemical inhibitors of nsP13.[3] Coronavirus disease-19 (COVID-19) is a universal target in a variety of institutions, producing pathogenic effects. It has been shown to be a multifaceted, multisystem, multiorgan disorder with roles involved in oxidative stress and inflammatory processes. Accordingly, along with the development of treatment, there are research results that the use of health functional food or health functional food for the prevention or treatment of SARS-CoV-2 infection will be an effective treatment method in the field of alternative and auxiliary treatment.[4] In addition, the identification of myricetin and scutellarein, novel chemical inhibitors of SARS coronavirus helicase and nsP13 in the past, was conducted. A study result showed that selected natural flavonoids such as myricetin and scutellarein could act as SARS-CoV chemical inhibitors.[5] Nuclear factor erythroid 2-related factor 2 (NRF2) plays an important role in a redox-sensitive transcription factor that protects organisms from various types of electrophiles or oxidizing agents. NRF2 levels remain low in normal cells but rise very high in cancers that develop chemical or radiation resistance. NRF2 maintains redox balance and plays an important role in autophagy, apoptosis, cell cycle progression, and stem cell differentiation, which can be attributed to the presence of all multiple binding proteins, the results of the study have shown.[6] Meanwhile, in Korea, genetic analysis, which was used for disease treatment or paternity confirmation through early diagnosis, has recently been introduced to the cosmetic field through Direct-To-Consumer (DTC) gene analysis. DTC genetic testing (GT) allows consumers to receive genetic testing directly without people visiting various medical institutions such as hospitals, and it is called DTC. In August 2020, "My own health food recommendation and sales service" suitable for individual health conditions and lifestyles passed the Korean Chamber of Commerce and Industry and the government's sandbox and was able to enter the market. The Ministry of Trade, Industry and Energy and the Sandbox Support Center of the Korea Chamber of Commerce and Industry announced that they had held the "Industrial Convergence Regulatory Special Exception Review Committee" in writing and approved 11 sandbox projects (exemption from regulations for a certain period for new businesses, deferment of regulations). In addition, to foster innovative medical devices, VR/AR-based medical device items were newly established, and the new medical technology evaluation system was improved. Currently, there are no separate licensed items, but the establishment of separate licensed items for convergence medical devices such as VR (Virtual Reality) and AR (Augmented Reality)-based cognitive behavioral therapy software is in progress.[7,8] Due to the circumstances of the times, the desire to live a healthy life has become common all over the world. People are getting more and more interested in a healthy life in the middle-aged and older people to be free from disease, to manage beautiful skin, and to prepare for an aging society. The focus is on the qualitative aspects of "how to live happily" and "how to live beautifully," rather than simply extending life in old age. Gradually, the definition of health and wellness in terms of beauty is evolving and being emphasized. Therefore, it is necessary to pay attention and support to the concept of various inner beauty and antioxidants of the middle-aged and elderly people related to immunity, and various studies that can be processed in combination are urgently needed.[9]

Therefore, this study intends to investigate the use of NRF2 through DTC-GT after COVID-19. DTC is possible, meaning that consumers can receive genetic tests directly without visiting medical institutions as the society rapidly shifts to a non-face-to-face society after COVID-19. Based on this 4th industrial revolution, it is expected that these data will be a helpful major research on NRF2 and NRF2 regulators of antioxidants using customized inner beauty by introducing convergence medical devices. In addition, this study is intended to be helpful as a reference material for activation of sales of customized cosmetics and customized inner beauty in the future, the right to know individual genetic information, the still incomplete domestic DTC-GTmarket, and agile response to rapidly changing market conditions.[10]

2 | MATERIALS AND METHODS

In May 2021, we proposed a narrative review as a new report and commentary. It was written with reference to keywords such as "Covid DTC Genetic Test", "Covid 4th industrial revolution," "Covid NRF2," and "Antioxidants." This study was performed by searching on PubMed, Google Scholar, Scopus, and ResearchGate. A total of 432 papers were retrieved, of which 40 were successfully included in this study. As a result, the disease management mechanism of NRF2, primary NRF2 function proven by past

disease cases, disease prevention management through DTC-GT, and health management through non-face-to-face application were presented in 4 tables.

3 | RESULTS

3.1 | Disease management mechanism of NRF2

The molecular mechanisms of various natural dietary compounds with chemopreventive effects have been intensively studied in various ways. Phase II detoxification and induction of antioxidant enzymes are oxidized through activation of Nrf2/ARE-dependent genes. It is recognized as one of the major cellular defense mechanisms against heterologous stress and currently represents an important chemopreventive mechanism.[11] The causes of many diseases in humans, including inflammation, cancer, cardiovascular and neurodegenerative disorders, are strongly related to environmental toxins. To counter the detrimental effects of the environment, mammalian and human cells have been studied to develop hierarchies of sophisticated sensing and signaling mechanisms that turn on or off endogenous antioxidant responses in various contexts. One of the cellular antioxidant responses is the cytoplasmic oxidative stress system (Nrf2-Keap1) activated by a variety of natural and synthetic chemopreventive agents, which function as antioxidant and carcinogen detoxifying enzymes. Keap1 anchors the Nrf2 transcription factor in the cytoplasm to target ubiquitination and proteasome degradation, thereby maintaining low levels of Nrf2, which mediates constitutive expression of Nrf2 downstream genes. When these cells are exposed to chemopreventive agents and oxidative stress, phosphorylation and redox modification signals of cysteine residues in Keap1 inhibit the enzymatic activity of the Keap1-Cul3-Rbx1 E3 ubiquitin ligase complex, thereby degrading or inhibiting Nrf2 ubiquitination.[12] As such, research results have been found that dietary phytochemicals induce the expression of enzymes involved in the antioxidant defense of cells and the removal and inactivation of electrophilic carcinogens. Induction of cytoprotective enzymes in various edible phytochemicals has cancer chemopreventive and chemoprotective activities. Nrf2 plays an important role in many stress responses and coordinated induction of genes encoding cell fusion enzymes and related proteins. These studies include NAD(P)H:quinone oxidoreductase-1, heme oxygenase-1, glutamate cysteine ligase, glutathione S-transferase, glutathione peroxidase, and thioredoxin etc. Nrf2 is sequestered in the vagina of cells as an inactive complex with the inhibitor Kelch-like ECH-related protein 1 (Keap1). Using the Nrf2-Keap1 system as a key molecular target, some representative recognition has highlighted cytoprotective gene expression induced by chemopreventive phytochemicals. Representative recognition using the Nrf2-Keap1 system as a key molecular target has been reported to highlight cytoprotective gene expression. Also, some of them are induced by chemopreventive phytochemicals.[13] Table 1 summarizes previous studies on antioxidants related to the central role of Nrf2.

3.2 | Primary NRF2 function demonstrated by past disease cases

In the past, SARS was caused by a novel coronavirus. Viral helicase, one of the components, has been studied in various ways for chemical SARS inhibitors. Characterization of the SARS coronavirus (SCV) helicase-nsP13, familial classification, and kinetic mechanism studies made novel findings in the potent inhibition of SARS helicase by natural flavonoids, myricetin, and scutellarein. A similar study also discussed novel chemical inhibitors of nsP13.[3] Myricetin and scutellarain were subjected to SARS coronavirus helicase, nsP13, fluorescence resonance energy transfer (FRET)-based double-stranded (ds) DNA unwinding to SARS coronavirus helicase, nsP13, and hepatitis C virus (HCV) helicase. Results were obtained for a novel inhibitory effect on the activity of NS3h. These results demonstrate that none of the compounds inhibited the DNA unfolding activity or ATPase activity of human HCV helicase protein. However, myricetin and scutellarein inhibited the SARS-CoV helicase protein by affecting ATPase activity *in vitro*. In addition, the study results showed that it had no effect on the unwinding activity of nsP13.[5] SARS and COVID-19 share the same characteristics as pneumonia and acute infectious diseases characterized by ARDS. These diseases are started by SARS-CoV-2, which belongs to the class of coronaviruses. MERS-CoV and SARS-CoV-1 are responsible for virus survival, replication, and spread within the host. It has positive sensing RNAs in its genome that link about 26 proteins. These viruses are transmitted through contact with aerosol droplets from an infected person. Exploring the use of these natural compounds could be a new alternative to COVID-19. In addition, there are studies showing that functional foods have immune-enhancing, antiviral, antioxidant, and anti-inflammatory effects. These studies include Zn, vitamin D, vitamin C, curcumin, cinnamaldehyde, probiotics, selenium, lactoferrin, and quercetin. These phytonutrients, in the form of food supplements, could serve to strengthen the immune system and prevent viruses.[14] SARS-CoV2 inhibition of NRF2 demonstrated novel antiviral and anti-inflammatory activities of 4-octyl-itaconate and dimethyl fumarate. Results obtained from patients with COVID-19 confirmed that the NRF2 antioxidant gene expression pathway was suppressed. In addition, the NRF2 agonist 4-octyl-itaconate (4-OI) and the clinically approved dimethyl fumarate (DMF) induce cellular antivirals that potently inhibit the replication of SARS-CoV2 in cell lines.[15] Table 2 summarizes previous studies on the pivotal role of Nrf2 in the therapeutic approach of disease.

3.3 | Preventive management of diseases through DTC-GT

DTC-GT, which first appeared in the early 2000s as a means of giving consumers access to their genetic information without the intervention of a physician, is called DTC-GT. Although controversial in the medical and regulatory fields, the early the model has created

TABLE 1 Previous Studies on Antioxidant Related to Pivotal Role of Nrf2

NO	Journal name	Author	Title	Discussion	References
1	*Journal of Biomol Ther (Seoul)*	Keum YS. 2012	Regulation of Nrf2-Mediated Phase II Detoxification and Antioxidant Genes	Functional importance of Keap1/Nrf2 protein modules in regulating ARE-dependent phase II detoxification and antioxidant gene expression.	[11]
2	*Methods Mol Biol*	Giudice A *et al.*2010	Review of molecular mechanisms involved in the activation of the Nrf2-ARE signaling pathway by chemopreventive agents	The discovery of multinuclear localization signals (NLS) and nuclear export signals (NES) in Nrf2 is also a consequence of the dynamic equilibrium of multivalent NLS and NES nuclear-cytoplasmic translocations of transcription factors.	[12]
3	*Planta Med*	Surh YJ *et al.*2008	Nrf2 as a master redox switch in turning on the cellular signaling involved in the induction of cytoprotective genes by some chemopreventive phytochemicals	Cytoprotective gene expression induced by some representative dietary chemopreventive phytochemicals using the Nrf2-Keap1 system as key molecular targets.	[13]
4	*Proc Natl Acad Sci USA*	Huang HC *et al.*2000	Regulation of the antioxidant response element by protein kinase C-mediated phosphorylation of NF-E2-related factor 2	Purified Nrf2 was phosphorylated in vitro by the catalytic subunit of PKC or by PKC immunoprecipitated from cell lysates.	[34]
5	*Free Radic Biol Med*	Jaiswal AK. 2004	Nrf2 signaling in coordinated activation of antioxidant gene expression	Nrf2 regulates transcription of enzymes involved in phase I and II detoxification of exogenous and endogenous products, NADPH regeneration and heme metabolism, as well as components of the glutathione and thioredoxin antioxidant systems.	[33]

TABLE 2 Previous Studies on the Pivotal Role of Nrf2 in Therapeutic Approaches of Diseases

NO	Journal name	Author	Title	Discussion	References
1	*Bioorg Med Chem Lett*	Yu MS *et al.* 2012	Identification of myricetin and scutellarein as novel chemical inhibitors of the SARS coronavirus helicase, nsP13	Selected naturally occurring flavonoids, including myricetin and scutellarein, may act as SARS-CoV chemoinhibitors.	[5]
2	*Biochem Pharmacol*	Keum YS *et al.* 2012	Development of chemical inhibitors of the SARS coronavirus: viral helicase as a potential target	Identification of novel chemical inhibitors of nsP13 in the context of recent findings on the potent inhibition of SARS helicase by the natural flavonoids, myricetin, and scutellarein.	[3]
3	*Free Radic Biol Med and Culture*	Jaiswal AK. 2004	Nrf2 signaling in coordinated activation of antioxidant gene expression	Additional nuclear factors, including small Mafs (MafG and MafK), large Maf (c-Maf), c-Fos, and Fra1 also bind to AREs and negatively regulate ARE-mediated gene expression.	[14]
4	*Nat Commun*	Olagnier D *et al.* 2020	SARS-CoV2-mediated suppression of NRF2-signaling reveals potent antiviral and anti-inflammatory activity of 4-octyl-itaconate and dimethyl fumarate	The NRF2 agonists 4-OI and DMF induce distinct IFN-independent antiviral programs that are broadly effective in restricting viral replication and inhibiting the proinflammatory response of human pathogenic viruses, including SARS-CoV2.	[15]
5	*Clin Transl Allergy*	Bousquet J *et al.* 2020	Nrf2-interacting nutrients and COVID−19: time for research to develop adaptation strategies	Nrf2-interacting foods and nutrients may rebalance insulin resistance and significantly affect COVID−19 severity during COVID−19 pandemic.	[36]

a new popularity among consumers.[16] The recent increase in public interest in genetics and genomics is driving the rapid growth of the DTC-GT. As yet, regulatory issues have limited true DTC-GTs that can be used without a physician's order. The future paradigm, however, has gradually shifted to a consumer-oriented GT model, in which patients research their own testing options and request specific genetic testing from healthcare providers.[17] DTC-GT has the advantage that it can be purchased directly through the Internet without a doctor's request or test approval. This makes it possible to retrieve genetic information outside the clinical context. It is true that there is still a lot of debate about the validity of these tests and their impact on individuals and people's knowledge and perceptions. However, research on systematic reexamination in which consumers directly conduct genetic tests based on the Internet is being conducted from various angles. As a result, the effect of DTC-GT on consumers' health perception and behavior has emerged as a new concern. However, no direct negative effects on health benefits for consumers were observed. Therefore, as the online market of DTC-GT is expected to grow rapidly, the study results suggest that awareness of the potential impact is important.[18] Precision medicine is well established to provide a wealth of novel genomic information data sets. However, the number of certified professionals in the United States is still small, with 4244 genetic counselors and 1302 clinical geneticists. A study was conducted to evaluate how to interpret genetic test results for 264 healthcare workers nationwide. As a result of the study, self-confidence and self-efficacy were confirmed by interpreting the results of the patient and genetic test. As a result of analyzing genetic tests sold DTC-GT, it was found that the percentage of accurate interpretation results (providers 74.4%, specialists 83.4%), age, past genetic test counseling experience, and report content were relatively high. The effectiveness of self-selection and the patient's readiness for counseling about the genetic outcome were higher in the expert group than in the provider group. Although DTC-GT is the best group of experts to support patients, a new conclusion has been confirmed that primary care providers can receive accurate interpretation of test results without the need for a specialist.[19] This suggests a better acceptance of the DTC-GT in the future. However, most counselors also tend to feel uncomfortable with the provision of these services. Only 6.9% of consumers said they were positive or very positive about themselves. For 40.1% of all respondents, a consumer study was conducted in the clinic for the purpose of reviewing the DTC-GT results. These findings show that most respondents are more likely to accept DTC-GT if DTC-GT is part of the genetic counseling process. Although 90.9% of respondents thought that participation of a genetic counselor would improve DTC-GT, only 31.2% "agree" or "strongly agree". Confirmation of these findings suggests that most respondents are more likely to accept DTC-GT if genetic counseling is part of the process. However, most counselors conclude that it is inconvenient to provide these services.[20] Table 3 summarizes disease prevention management through DTC -GT.

3.4 | Health management through applications in the non-face-to-face era

The global economy is now in serious trouble due to COVID-19. In this context of the times, the non-face-to-face era is expanding. Effective consumption promotion in the future is seen as an important task to counter the impact of the epidemic. With the popularization of mobile shopping in the non-face-to-face society, shopping behavior is no longer limited by time and space.[21] There are results of a study on mobile shopping awareness and development potential of COVID-19 customized cosmetics conducted for women in their 40s and 60s in Korea. This study focused on the recognition and development potential of customized cosmetics in mobile shopping as the country rapidly shifted to a non-face-to-face society due to COVID-19. As a result of the study, it was revealed that in the unexplored era after COVID-19, the possibilities of developing customized cosmetics through mobile shopping will be limitless. There was an opinion that app development should be carried out additionally due to the 4th industrial revolution.[22] Even in a systematic evaluation study of popular and commercially available mobile apps providing healthy family food, modern households face conflicting demands for time and resources. This has the potential to degrade the quality of children's and families' diets. Behavioral support providing parents with healthy food could alleviate this problem with innovative nutritional interventions. Studies have shown that mobile apps can provide these interventions because they can provide actionable behavioral support remotely, interactively, and in context.[23] Mobile apps are widely used in the medical field. The quality of clinical technology mobile apps is systematically searched for and the quality of apps that meet specified criteria is widely used to measure general app quality. These mobile app rating scales (MARS) and their values are being measured and studied.[24]The importance of mobile applications is being emphasized as modern society is undergoing overall social development and change called the mobile revolution. Governments and IT companies are launching mobile applications in various fields. Attention is focused on the medical field. Applications in the medical field are gradually expanding into fields such as exercise, eating habits, and safety, and the proportion is also increasing. However, there is a trend of overlap-ping development with mostly limited topics. In addition, there is currently no precedent for separately naming and classifying applications in the medical and health fields in the domestic mobile content industry. In this situation, it is necessary to establish an accurate classification or category.[25]A mobile healthcare application is a healthcare software application that runs on mobile devices such as smartphones and tablet computers. Mobile healthcare applications have a lot of potential, such as managing and monitoring the daily lives of patients with chronic diseases. As a preliminary experiment, the possibility of using the application in daily life was confirmed.[26] Table 4 summarizes health management through non-face-to-face applications.

TABLE 3 Preventive Management of Diseases through DTC-GT

Author	Covolo L *et al.* (2015)	Ramos E *et al.* (2018)	McGrath SP *et al.* (2019)	Hsieh V *et al.* (2020)	Lee J *et al.* (2021)
Title	Internet-Based Direct-to-Consumer Genetic Testing: A Systematic Review.	The dawn of consumer-directed testing.	Are providers prepared for genomic medicine: interpretation of Direct-to-Consumer genetic testing (DTC-GT) results and genetic self-efficacy by medical professionals.	Direct-to-consumer genetic testing companies tell their customers to "see a genetic counselor." How do genetic counselors feel about direct-to-consumer genetic testing?	DTC genetic test for customized cosmetics in COVID−19 pandemic: Focused on women in their 40s and 60s in Seoul, Republic of Korea, Republic of Korea.
Discussion	Since the online market of DTC-GT is expected to grow, it is important to remain aware of a possible impact.	Despite many complex questions and challenges, this market represents an opportunity for the genetics community to address unmet needs.	Specialists remain the best group to assist patients with DTC-GT, however, primary care providers may still provide accurate interpretation of test results when specialists are unavailable.	If genetic counseling was part of the process, most respondents would be more receptive to the DTC-GT, but the majority of counselors felt uncomfortable providing this service.	After the COVID−19 pandemic, it was confirmed for the first time that the consumption of customized inner beauty formulations and the use of customized cosmetics would be more effective.
Journal name	*J Med Internet Res*	*Am J Med Genet C Semin Med Genet*	*BMC Health Serv Res*	*J Genet Couns*	*J Cosmet Dermatol*
References	[18]	[17]	[19]	[20]	[10]

TABLE 4 Health Management through Applications in the Non-Face-To-Face Era

Author	Shin H *et al.* (2015)	Kim JH *et al.* (2016)	Mandracchia F *et al.* (2020)	Gladman T *et al.* (2021)	Lee J *et al.* (2021)
Title	Status of health-related applications and ways to improve.	Study on Play Effect Analysis of FUN Concept Handicraft and its Effectiveness Evaluation - Focusing on interior decoration tools and furniture design.	Mobile Phone Apps for Food Allergies or Intolerances in App Stores: Systematic Search and Quality Assessment Using the Mobile App Rating Scale (MARS).	Measuring the Quality of Clinical Skills Mobile Apps for Student Learning: Systematic Search, Analysis, and Comparison of Two Measurement Scales.	Recognition and the development potential of mobile shopping of customized cosmetic on untact coronavirus disease 2019 period: Focused on 40's to 60's women in Seoul, Republic of Korea.
Discussion	A definition and classification system for health-related applications was proposed, and problems of health-related applications were derived through a current status survey to lead the improvement of various and high-quality health-related applications.	Mobile healthcare applications have a lot of potential in managing and monitoring the daily lives of patients complaining of chronic diseases.	It can help improve the innovativeness and applicability of future food allergy and intolerance apps.	Mobile apps are widely used in healthcare, increasing the need for a simple way to determine the quality of apps.	In the untact era after Corona 19, the possibility of developing customized cosmetics through mobile shopping is limitless, and it is judged that various marketing strategies will be supported in the future.
Journal name	*FDC Law Study*	*Korea Design Trend Society*	*JMIR Mhealth Uhealth*	*JMIR Mhealth Uhealth*	*J Cosmet Dermatol*
References	[25]	[26]	[23]	[24]	[23]

4 | DISCUSSIONS

The virus causes COVID-19, a disease characterized by shortness of breath, fever, and pneumonia, which can be fatal to people's bodies. SARS-CoV-2 has similar characteristics to past human coronaviruses. It has the same genomic similarity. So, just like coronavirus, SARS-CoV-2 is transmitted through droplet inhalation and interaction with contaminated surfaces. Candidate vaccines for viruses are being developed through vaccine trials worldwide. In addition, various drugs for possible treatment and prevention are being considered. As a result, a wide range of vaccines are being developed and tested at an unprecedented rate through close collaboration between academia, industry, and government sectors.[27,28,29] This is a multifaceted effort worldwide to develop new treatments and protect public health. Research is underway to develop a successful vaccine to prevent another future COVID-19. An exit strategy for returning to daily life is urgently needed. Despite various efforts, there is still no sign of a global resolution of COVID-19.[30] A wide range of heterologous metabolic enzymes catalyze both phase 1 (oxidation and reduction) and phase 2 biotransformation (conjugation) reactions involving the activation or inactivation of carcinogens. Modulation of various antioxidant response elements (ARE) such as glutathione S-transferase, NAD(P)H-quinone oxidoreductase-1, UDP-glucuronosyltransferase, gamma-glutamate cystein ligase, and hemeoxygenase-1. The gene product serves this detoxification and antioxidant function. It protects cells from genotoxic damage. Transcription of ARE-inducing genes is regulated by the nuclear transcription factor erythrocyte 2p45 (NF-E2)-related factor 2 (Nrf2) with sequestered from the cytoplasm by Kelch-like ECH-related protein 1 (Keap1). This could lead to a two-step detoxification or de novo synthesis of antioxidant genes via the Nrf2-ARE key signaling pathway, allowing chemoprevention to protect DNA and other important cellular molecules.[31] Studies have shown that Jun protein-related Nrf2 and Nrf1 regulate antioxidant response element-mediated expression and coordinated induction of genes encoding detoxification enzymes. From these studies, it can be confirmed that nuclear transcription factors Nrf2 and Nrf1 are related to Jun (c-Jun, Jun-B, and Jun-D) proteins. It upregulates ARE-mediated expression and regulates the induction of antioxidants and detoxifying enzymes in response to xenobiotics.[32] Studies have shown that antioxidant response element (ARE)-mediated expression and coordinated induction of antioxidant enzymes play an important role in the protection of chemically induced oxidative electrophilic stress. NF-E2-related nuclear factors (Nrf1 and Nrf2) bind to AREs and regulate ARE-mediated gene expression and induction. Nrf2 is more potent than Nrf1 in the activation of ARE-regulated gene expression. Nrf2 is maintained in the cytoplasm by the inhibitor INrf2. An increase in oxidative electrophilic stress with chemical exposure leads to activation of protein kinase C (PKC) and other cytoplasmic factors. In addition, additional nuclear factors, including small Mafs (MafG and MafK), large Maf (c-Maf), c-Fos, and Fra1, also bind to AREs, causing negative regulation of ARE-mediated gene expression.[33] Cellular responses coordinated to oxidative stress occur in part through cis-acting sequences known as antioxidant response elements (AREs). NF-E2-related factor 2 (Nrf2), a member of the Cap'n'Collar family of basic region-leucine zipper (bZIP) transcription factors, has been implicated as an essential component of the ARE-binding transcription complex. However, the signaling pathways leading to activation are not yet clear. In addition, there is also a study result showing that PKC precipitated from cells treated with tBHQ or betaNF showed enhanced activity against Nrf2. These findings show that the PKC pathway plays an important role in ARE-mediated gene expression.[34] Research has been done on whether NRF2 activation could be a strategy against COVID-19. In that study, exacerbated proinflammatory cytokine resecretion (cytokine storm) and T lymphocyte loss (leukopenia) were the most aggressive symptoms. It has been proposed that a multifaceted anti-inflammatory strategy based on the pharmacological activation of nuclear factor erythroid 2p45-related factor 2 (NRF2) could be deployed against viruses. These strategies serve as powerful cell protections by restoring redox and protein homeostasis, promoting resolution of inflammation, and promoting recovery. In addition, various studies have been conducted, such as NRF2 activators such as sulforaphane and bardoxolonemethyl.[35] Research has been conducted to develop nutrients that interact with Nrf2 and adaptation strategies for COVID-19. As a result, some very low-mortality environments, such as East Asia, Central Europe, the Balkans, and Africa, had a common feature of consuming high intake-related fermented foods, such as Nrf2 nuclear factor (erythrocyte-derived 2). In this study, antioxidant transcription factors and Nrf2-interacting nutrients (berberine, curcumin, epigallocatechin gallate, genistein, quercetin, resveratrol, and sulforaphane) all acted similarly. It has been shown to reduce insulin resistance, endothelial damage, lung damage, and cytokines. The suggestion that it could have a serious impact on COVID-19 is encouraging. Additionally, foods and nutrients that interact with Nrf2 re-modulate insulin resistance. Therefore, consuming these foods may restore the optimal natural balance to the Nrf2 pathway, which may affect COVID-19 severity relief.[36] Additionally, research suggests that TRPA1 may be activated by reactive oxygen species and thus may be upregulated in COVID-19. TRPA1 and TRPV1 can be activated by many nuclear factors (erythrocyte-derived 2) (Nrf2) that interact with food, including stimulatory compounds that desensitize the channel. Interactions between Nrf2-related nutrients and TRPA1 and TRPV1 may partially alleviate the severity of some COVID-19 symptoms. The regulation of TRPA1 and TRPV1 by Nrf2 is not yet clear, but it can be confirmed with very limited clinical evidence. It has also been suggested that COVID-19 may reduce the severity of symptoms of TRPA1 and TRPV1 caused by some components of food and may provide a strategy for new treatments.[37] A randomized trial study of electronic personal health records for patients with severe mental illness was also conducted. This study evaluated the impact on quality of care in community mental health settings. As a result, the study found that the presence of an individual's health record significantly improved the quality of medical services

and increased the use of medical services by patients when evaluating the quality of medical services, patient activation, service use, and health-related quality of life.[38] The use and scope of DTC-GT, also known as consumer-led direct genetic testing, are increasing. As a result, consumers can receive genetic counseling to understand the consequences and determine their impact on health care. Recently, these studies have been multifaceted. In these studies, people who requested genetic counseling after receiving DTC-GT results were interviewed, and their motivations, expectations, and experiences were explored. As a result, it was reported that DTC-GT results could be valid and potentially impactful in health care. They wanted a more thorough explanation in "lay terminology" that combined the results with family and personal health records and "game plans." Consumers reported concerns about clinic visits for DTC-GT genetic counseling sessions.[39] Genomic data, as well as uncertainty and rumors surrounding the business practices of DTC-GT service providers, showed clinical value and sensitivity. As a result, DTC-GT has received considerable criticism from researchers and practitioners. However, research in this area has focused on the ethical and legal implications of providing genetic testing directly to consumers. The business of the DTC-GT market has recently witnessed a surge in DTC-GT services due to the development of genomic data collection and analysis technology. In addition, the era of the "genetic revolution", which analyzes information about an individual's disease and physical characteristics through genes, is now being opened. This is because the price and period of analysis are rapidly decreasing due to the development of genetic analysis technology in recent years. Human DNA contains genes in 3 billion pairs of base sequences. This is because of the great advances in the computer's ability to analyze it. In line with this era, the government hasalso implemented the industrial convergenceregulatory sandbox system for certification and permit standards for new products and services related to genetic testing. A regulatory sandbox is a system that exempts or suspends existing regulations for a certain period until a new product or service is launched in a new industry/technology field. In Korea, this sandbox has made it possible to perform genetic tests that can be easily performed in everyday life. In June 2016, the market for genetic analysis services and DTC products was opened. In Korea, the DTC-GT allows the processing of 56 wellness items related to individual characteristics with regards to 13 types of skin-related genes such as skin aging, freckles, pigmentation, tanning reaction, stretch marks, and acne outbreaks and 13 types of health care-related genes, etc. and health and analyzes the personal genetic DTC test kit products provided in Korea from the point of experience design. It is very meaningful to propose the most suitable genetic test kit product, from test application to actual sample collection and return. Genetic test kit products developed based on user experience will be able to utilize basic data for efficient and popular personal genetic testing in the future. It is also expected to help form a new medical culture and improve public health care.[40]A randomized trial study of personal health records from Behavioral Health Homes mobile tested whether the application improved the quality of health care for individuals receiving care in these settings. Severe mental illness was found across two behavioral health centers to receive either a mobile personal health record application or routine care, and 311 participants with one or more cardiac metabolic risk factors were enrolled. The secure mobile personal health record (mPHR) app provided intervention group participants key information on diagnostics, medications, and laboratory test values and enabled them to track health goals. The use of the mPHR app showed statistically significant results for the quality of care in individuals with severe psychiatric disorders and comorbid cardiac metabolic disorders. However, it has been clinically reported to be associated with a moderate differential benefit.[41] In addition, during the COVID-19 pandemic, research on DTC-GT for customized cosmetics underlined the evolution of DTC-GT since then. As a result, it was confirmed for the first time that the consumption of customized inner beauty formulations and the use of customized cosmetics would be more effective. Based on the above meaningful research results, it has been announced that it is necessary to study the combined effect of customized inner beauty products and customized cosmetics in the global DTC-GT market.[10]

5 | CONCLUSIONS

Therefore, this study is also evolving the definition of health sustainability, well-being, and well-dying after the global COVID-19 pandemic. Accordingly, we considered the use of NRF2 through DTC -GT in the non-face-to-face era. To summarize the above important research results, it is necessary to introduce convergence medical devices based on the 4th industrial revolution in the still insufficient global DTC-GT market. It is hoped that this study will serve as key data to help develop the potential of antioxidants as NRF2 modulators in customized inner beauty products and customized cosmetics. Due to the increase in mobile usage in the future, it is judged that additional and various follow-up studies on app development are needed.

CONFLICT OF INTEREST

The authors of this manuscript do not have any conflicts of interest to disclose.

ETHICAL APPROVAL

The conducted literature review did not require the agreement of the bioethics committee.

AUTHOR CONTRIBUTIONS

Jinkyung Lee and Ki Han Kwon involved in conception or design of the work, interpretation, drafted the article, and critically revised of the article. All authors finally approved the version to be published.

DATA AVAILABILITY STATEMENT

The findings of this study are available from the corresponding author upon reasonable request.

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