Mapping Pharmacological Network of Multi-Targeting Litchi Ingredients in Cancer Therapeutics

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Considerable pharmacological studies have demonstrated that the extracts and ingredients from different parts (seeds, peels, pulps, and flowers) of Litchi exhibited anticancer effects by affecting the proliferation, apoptosis, autophagy, metastasis, chemotherapy and radiotherapy sensitivity, stemness, metabolism, angiogenesis, and immunity via multiple targeting. However, there is no systematical analysis on the interaction network of “multiple ingredients-multiple targets-multiple pathways” anticancer effects of Litchi. In this study, we summarized the confirmed anticancer ingredients and molecular targets of Litchi based on published articles and applied network pharmacology approach to explore the complex mechanisms underlying these effects from a perspective of system biology. The top ingredients, top targets, and top pathways of each anticancer function were identified using network pharmacology approach. Further intersecting analyses showed that Epigallocatechin gallate (EGCG), Gallic acid, Kaempferol, Luteolin, and Betulinic acid were the top ingredients which might be the key ingredients exerting anticancer function of Litchi, while BAX, BCL2, CASP3, and AKT1 were the top targets which might be the main targets underlying the anticancer mechanisms of these top ingredients. These results provided references for further understanding and exploration of Litchi as therapeutics in cancer as well as the application of “Component Formula” based on Litchi’s effective ingredients.

Keywords: litchi, cancer, multi-ingredients, multi-targets, network pharmacology

INTRODUCTION

Cancer is one of the most serious public health problems globally. In 2018, approximately 18.1 million new cancer cases and 9.6 million cancer-related deaths occurred in the world (Bray et al., 2018). There is an urgent need for a more effective therapy. Traditional Chinese medicine (TCM) has been used for thousands of years in Asia for its good efficacy and compliance, and this also made it an important supplemental medicine in cancer treatment (Xiang et al., 2019). Comparing with the current “one drug, one target” mode, TCM has the feature of “multiple active ingredients, multiple targets” (Li and Zhang, 2013). Given that cancer is a complex disease which alters a range of cellular
and molecular processes, TCM may hold the advantage of targeting multiple cancer-related molecules simultaneously with potential synergistic effects. However, as a result of the feature of “multiple ingredients, multiple targets”, herbs can potentially interact with prescription medications like when cancer patients use plant-based regimens with chemotherapy (Yeung et al., 2018; Parvez and Rishi, 2019; Pezzani et al., 2019). Therefore, the potential risk of using TCM as complementary medicine should be considered for maximum safety and efficacy.

*Litchi chinensis Sonn* (Litchi), a member of Litchi, Sapindaceae family, is a subtropical evergreen plant which has been widely cultivated as an economic cultivar for its delicious taste and rich nutrition fruitage in China, Philippines, Indonesia, and Vietnam (Mitra, 2002; Menzel et al., 2005). In China, Litchi seeds were used as an analgesic agent for the alleviation of neuralgia, orchitis, testicular swelling, hernia, gastralgia, lumbago, abdominal pain, etc. (Lan and Lan, 2011). The decoctions of Chinese herbal formula containing Litchi seeds were used as indigenous remedies for urologic neoplasms including prostate cancer, bladder cancer, and renal carcinoma (Shi, 2004; Wang, 2011c). Moreover, a considerable amount of studies have shown that in addition to Litchi seeds, the extracts and ingredients from other parts (peels, pulps, and flowers) of Litchi can exert multiple pharmacological actions which have the anti-inflammatory (Das et al., 2016), anti-oxidative (Lee et al., 2016), anti-bacterial (Yang et al., 2016), anti-viral (Gangethi et al., 2010; Xu et al., 2010a), anti-liver injury, and immune-enhancing effects (Noh et al., 2011; Huang et al., 2014a; Yamanishi et al., 2014; Huang et al., 2014b; Huang et al., 2016a; Su et al., 2016; Xiao et al., 2017; Queiroz et al., 2018). Furthermore, there was accumulating evidence indicating that the extracts and compounds from Litchi exhibit anticancer effects by targeting multiple proteins and signal pathways involved in cancer cell proliferation, metastasis, angiogenesis, apoptosis, autophagy, etc. However, current studies are limited to the traditional research method of identifying “single-drug, single-target, and single-pathway”, which failed to reflect the “multiple ingredients-multiple targets-multiple pathways” anticancer effects of Litchi. In order to elucidate its multiple modes of action, network pharmacology and bioinformatics were employed in this study as a powerful approach (Zhang et al., 2019a) to systematically analyze the complicated interactions between Litchi ingredients and confirmed targets based on published research results. This study has provided a solid base for the further exploration of its anticancer effects.

### METHODS

We collected the anticancer ingredients and targets of Litchi based on original published articles. In order to systematically analyze the complex relationships between these anticancer ingredients and their targets, an interaction network was constructed by network pharmacology approach. All networks maps were visualized and analyzed by Cytoscape 3.2.1 (http://www.cytoscape.org/). As shown in the ingredient-target network (Figures 1A, 2A, 3A, 4A, and 5), the oval nodes represent ingredients, the rectangle nodes represent targets and each edge linking an ingredient to a target indicates a regulator-target relationship. In Figures 1A–4A, the targets distributing in the inner orange circle (rectangle) can be modulated by multiple ingredients rather than a single ingredient. The “degree” is an important parameter for the network pharmacology approach, which represents the number of related nodes to a particular node in the network. The greater the degree of a node, the more biologically important it is. Therefore, the top ingredients and targets were screened out by the Network Analyzer in Cytoscape based on the major parameter of “degree”. To further explore the core biological processes of the top targets involved, we performed KEGG pathway enrichment analysis (http://www.kegg.jp/) and screened out the top signal pathways based on the P-value. The relationships among top targets, corresponding ingredients and signal pathways were analyzed by combining Cytoscape 3.2.1 with KEGG pathway enrichment analysis. In order to test the reliability of the top ingredient-target interactions and explore the accurate binding modes, we performed molecular docking analysis by using surflex module of Sybyl X2.0. A total score greater than 6 represents good protein-ligand binding. The crystal structures of proteins (targets) were extracted from Protein Data Bank (https://www.rcsb.org/).

### RESULTS

#### Ingredients From Litchi

Litchi contains a variety of natural products, such as anthocyanins, flavonoids, phenolic acids, terpenes, fatty acids, sterols, lignans, coumarins, and esters. A total of 110 compounds (32 Anthocyanins, 32 Flavonoids, 9 Phenolic acids, 9 Tocotrienols, 8 Lignans, 4 Alcohols, 4 Sterols, 3 Triterpenes, 3 Fatty Acids, 2 Esters, 2 Glycosides, 1 Furfurals, 1 Coumarins) isolated from Litchi have been reported, which were summarized in Table 1 according to the parts (peels, pulps, seeds, leaves, and flowers) of Litchi, with their molecular formulae, structure category and corresponding reference (Ref). As shown in Table 1, various kinds of chemical constituents were isolated from its peels (28 compounds), pulps (12 compounds), seeds (49 compounds) leaves (28 compounds), and flowers (1 compound). Among them, we identified flavonoids and anthocyanins which were mostly found in Litchi peels, seeds, and leaves to be the main compounds.

#### The Multi-Targeted Anticancer Effects of Litchi Ingredients

We summarized the confirmed anticancer ingredients of Litchi by going through each original published articles and found that 19 compounds (6 Anthocyanidins, 7 Flavonoids, 3 Phenolic acids, 2 Sterols, 1 Triterpenes) might inhibit cancer development through multifunctional mechanisms including regulation of cell proliferation, apoptosis, metabolism, metastasis, angiogenesis, stemness, and immunity. The
anticancer ingredients with their corresponding effects, molecular targets, and cancer types were listed in Table 2. We then discovered that a single component could have a range of targets and different components had overlapping molecular targets, hence they formed a complicated regulatory network. In order to unravel this intricate web of interactions, we applied network pharmacology method to analyze the anticancer effects of Litchi from a perspective of system biology.

**Inhibition of Cancer Cell Proliferation**

Sustained proliferation is a hallmark of cancer cells, and the restoration of dysregulated signaling pathways has always been a target for cancer treatment. The extracts from Litchi peels, pulps, seeds, leaves have been shown to inhibit the proliferation of a variety of cancer cells (Huang et al., 2015a; Gong et al., 2018; Zhao et al., 2019a). The 13 anti-proliferative compounds identified from Litchi and 100 regulated targets were summarized in Table S1. The detailed analysis of the top active ingredients, corresponding targets, and signal pathways affected was shown in Figure 1.

In total, this ingredient-target network (Figure 1A) was consisted of 113 nodes (Table S1) and the mean degree of all nodes in the network was 3.080. Overall, 3 out of the 13 anticancer compounds (Figure 1A) had high degree distributions (kaempferol: degree=39, Epigallocatechin gallate (EGCG): degree=36, gallic acid: degree=22) and all of them modulated more than 20 targets, which marked their pharmacological importance. Notably, those targets have more than one regulator (Table S2). Apart from 1 target that was regulated by 10 ingredients, 4 targets were regulated by over 5 ingredients and 28 targets were regulated by 2–4 ingredients (Figure 1B). Further, the 4 top targets (MAPK1, CDKN1A, MAPK14, AKT1) were screened out from Figures 1A, B, whose degree values were more than two folds of the median degree of

![FIGURE 1](image-url)
all nodes in the network. This suggested that multiple ingredients could potentially exert synergistic anti-proliferation effects. In particular, the interactions among the above 4 top targets and Litchi ingredients (Table S3) were analyzed in Figure 1C. With the results shown in Figure 1C, we could conclude that there were 11 out of 13 ingredients that could regulate the top targets with anti-proliferative effects. It was also confirmed that the top 4 targets played an important role in the anti-proliferative process. Particularly, kaempferol, EGCG, and gallic acid could regulate all the top targets, and this conclusion was similar to that in Figure 1A where 3 ingredients mentioned above had outstanding pharmacological significance. To further clarify the anticancer mechanism of Litchi ingredients, the pathway enrichment analysis based on above 4 top targets was performed. There were 63 signaling pathways involved in the anti-proliferation effects of Litchi ingredients (Figure 1C and Table S3), and FoxO, VEGF, Prolactin, ErbB, HIF-1, Toll-like receptor, TNF, Rap1, MAPK, and PI3K-Akt signaling pathways were the top 10 pathways according to their P values (Figure 1D). All of the 4 top targets were elements of FoxO signaling pathway and 3 out of the top 4 targets were elements of other 9 top pathways. It indicated that these top 10 pathways might be the major signaling pathways that are responsible for the anti-proliferation effects of Litchi.

Induction of Cancer Cell Apoptosis and Autophagy
Apart from uncontrollable proliferation, resistance to cell death is another strategy employed by cancer cells to fuel its growth.
Cancer cells have evolved a series of strategies to inhibit cell death while Litchi ingredients have been reported to have pro-apoptosis and pro-autophagy effects (Hsu et al., 2012a; Emanuele et al., 2018). Hence, we summarized data from literature and constructed the network (Figure 2A) based on 18 ingredients from Litchi and 138 targets (Table S4) which related to cell apoptosis and autophagy. The network was consisted of 156 nodes and 283 edges altogether, representing the extensive interactions among 18 ingredients and 138 targets (Table S4).

Not surprisingly, we found that the mean degree of node was 3.679 based on the topological analysis, suggesting that it was common for ingredients to have multiple targets. By referring to the mean degree, we identified 6 top ingredients with a median degree ≥20, namely luteolin, EGCG, kaempferol, gallic acid, betulinic acid, and chlorogenic acid, with the top 2 having over 40 targets. Hence, we concluded that those top 6 ingredients were likely to be crucial components in promoting apoptosis and autophagy. Further, in order to clearly elucidate if these targets were regulated by multiple ingredients, another analysis was performed in Figure 2B, which showed that there were 3 targets regulated by over 10 ingredients, 9 targets were regulated by 5–10 ingredients and 33 targets were regulated by more than 2 ingredients (Figure 2B and Table S2). From Figures 2A, B, we next screened out the top 6 targets (BAX, BCL2, CASP3, CASP9, TP53, AKT1) based on their degrees in the ingredient-target network. As shown in Figure 2C and Table S5, all of the top 6 targets could be regulated by luteolin and EGCG, and this implied that they had multiple anticancer activities. In addition, all the 18 ingredients involving in apoptosis and autophagy interacted with the top targets, which consolidated the importance of these top targets. KEGG enrichment analysis based on these 6 top targets showed that 39 signaling pathways...
were involved in the effects of inducing cancer cell apoptosis and autophagy (Figure 2C and Table S5), while p53, Neurotrophin, Sphingolipid, PI3K-Akt, Thyroid hormone, MAPK, VEGF, HIF-1, TNF signaling pathway and Adrenergic signaling in cardiomyocytes were the top 10 pathways (Figure 2D). Four out of these top 6 targets were elements of p53, Neurotrophin, Sphingolipid, and PI3K-Akt signaling pathways, which indicates that these four signaling pathways might be the major pathways responsible for anticancer effect by inducing apoptosis and autophagy.

**Inhibiting Metastasis**

Metastasis is another target in cancer therapeutic development due to its lethality (Liu et al., 2017). Litchi seed extracts could attenuate migration and invasion capabilities of PC3 and DU145 cells (Guo et al., 2017). Nine anti-metastasis ingredients of Litchi and 99 corresponding targets were listed in Figure 3A. We found that the mean degree of nodes in the network was 3.296. Then we screened out 4 top ingredients, namely EGCG, gallic acid, luteolin, and PA, with a median \( \geq 20 \) degrees, which acted on 41, 29, 22, and 21 targets respectively. Therefore these 4 top ingredients identified were likely to be crucial bioactive components to inhibit metastasis. In addition, among the 99 targets, the network showed that MMP2 had the largest number of ingredient-target interactions (degree value of 8), followed by MMP9 (degree value of 7), making them likely to perform anti-metastasis functions. The remaining targets with lower degree and less than two folds of the mean degree of all nodes were also included. Then, the targets regulated by multiple ingredients were analyzed with a similar approach for more information. As shown in Figure 3B and Table S2, MMP2 and MMP9 were

![Image of Ingredient-Target Network of Litchi Sensitizing Chemotherapy and Radiotherapy](image-url)
regulated by 8 and 7 ingredients respectively, followed by another 6 targets regulated by up to 5 ingredients and 26 targets regulated by 2 to 4 ingredients. The “ingredients-top targets-pathways” network (Figure 3C and Table S7) was constructed for the purpose of confirming the significance of top 2 targets, and this network indicated that as much as 8 ingredients exerted the anti-metastasis function through modulating MMP2 and MMP9. However, the signaling pathways enriched by KEGG based on 2 top targets merely included bladder cancer, estrogen signaling pathway, leukocyte transendothelial migration, proteoglycans in cancer and pathways in cancer. Both the top 2 targets were elements of these 5 pathways (Figures 3C, D and Table S6), which indicated these 5 pathways might be the key anti-metastasis mechanism of Litchi.

Sensitizing Chemotherapy and Radiotherapy
Chemotherapy and radiotherapy are two of the most common cancer treatments. Despite their clinical efficacy in clearing cancer cells, therapeutic resistance often inevitably occurs. Another reported effect of Litchi was that it sensitized chemotherapy and radiotherapy. Here we identified 12 compounds from Litchi and 106 corresponding molecular targets responsible for this function (Table S8), with the detailed interactions of the top ingredients, targets and signal pathways shown in the Figure 4. From Figure 4A, we screened out 5 top ingredients with a median degree ≥20, including luteolin, EGCG, kaempferol, gallic acid, and betulinic acid, which linked to as much as 35, 34, 25, 22, and 21 targets respectively. Not surprisingly, the mode of “multi-ingredients, multi-targets” was confirmed again by identifying CASP3, BAX, and BCL2 as the top targets, which had the degree values of 9, 8, 6 respectively, which were more than two folds of the median degree of all nodes in the network. In addition, there were another 32 targets regulated by more than 2 ingredients (Figure 4B and Table S2), which implied that Litchi ingredients could overcome chemo- and radio-resistance through a “multi-compounds, multi-targets” mode with potential synergistic effects. The “ingredients-top targets-pathways” network (Table S9) confirmed the importance of CASP3, BAX, and BCL2 further. In Figure 4C, 10 out of 12 ingredients that were involved in sensitizing chemotherapy and radiotherapy exerted anticancer activity through regulating the 3 top targets. Moreover, KEGG enrichment analysis of top 3
### TABLE 1 | Compounds Isolated from L. chinensis.

| Parts   | No | Ingredients                        | Formula          | Compound yield (mg/100g) | Category               | Ref                  |
|---------|----|------------------------------------|------------------|--------------------------|------------------------|----------------------|
| Peels   |    | Cyanidin-3-rutinoside              | C_{27}H_{31}O_{15} | 1.29-19.11               | Anthocyanins           | (Li et al., 2012)   |
|         | 2  | Cyanidin-3-glucoside               | C_{21}H_{21}O_{11} | 0.80-1.80                | Anthocyanins           | (Li et al., 2012)   |
|         | 3  | Quercetin-3-glucoside             | C_{21}H_{20}O_{12} | 5.00                     | Anthocyanins           | (Ma et al., 2014)   |
|         | 4  | Malvidin-3-glucoside              | C_{23}H_{25}O_{12} | 0.67-9.98                | Anthocyanins           | (Li et al., 2012)   |
|         | 5  | Epigallocatechin gallate (EGCG)   | C_{22}H_{28}O_{11} | /                        | Anthocyanins           | (Xie, 2017)         |
|         | 6  | Dehydroepicatechin A              | C_{20}H_{20}O_{12} | 0.50                     | Anthocyanins           | (Ma et al., 2014)   |
|         | 7  | Procyanidin A2                    | C_{30}H_{24}O_{12} | 68.30                    | Anthocyanins           | (Sarni-Manchado et al., 2000) |
|         | 8  | Proanthocyanidin A1               | C_{21}H_{22}O_{12} | 0.64                     | Anthocyanins           | (Ma et al., 2014)   |
|         | 9  | Epicatechin-(4β–8,2β–O–7)-epicatechin | C_{21}H_{20}O_{12} | 1.02                    | Anthocyanins           | (Zhang et al., 2003) |
|         | 10 | Proanthocyanidin B2               | C_{20}H_{22}O_{12} | 0.48                     | Anthocyanins           | (Zhang et al., 2003) |
|         | 11 | Proanthocyanidin B4               | C_{20}H_{18}O_{12} | 0.30                     | Anthocyanins           | (Ma et al., 2014)   |
|         | 12 | Bis(8-epicatechinyl) methane      | C_{21}H_{20}O_{12} | 0.06                     | Anthocyanins           | (Ma et al., 2014)   |
|         | 13 | 8-(2-pyrrolidinone-5-yl)-epicatechin | C_{21}H_{20}O_{12} | 0.16                    | Anthocyanins           | (Ma et al., 2014)   |
|         | 14 | Epicatechin-8-C-(β-D-glucopyranoside | C_{21}H_{20}O_{12} | 0.08                    | Anthocyanins           | (Ma et al., 2014)   |
|         | 15 | Naringenin-O-(2,6-O-α-L-rhamnopyranosyl)-β-D-glucopyranoside | C_{33}H_{40}O_{20} | 0.30 | Anthocyanins | (Ma et al., 2014) |
|         | 16 | Epigallocatechin (EGC)            | C_{17}H_{24}O_{12} | 97.30                    | Anthocyanins           | (Zhang et al., 2003) |
|         | 17 | Rutin                            | C_{20}H_{22}O_{12} | 0.44                     | Flavonoids             | (Ma et al., 2014)   |
|         | 18 | Epicatechin                       | C_{16}H_{18}O_{12} | /                        | Flavonoids             | (Zhou et al., 2011) |
|         | 19 | (-)-Epicatechin (EC)              | C_{16}H_{18}O_{12} | 0.22                     | Flavonoids             | (Ma et al., 2014)   |
|         | 20 | (-)-Galloic acid (GC)             | C_{16}H_{20}O_{12} | 22.90                    | Flavonoids             | (Zhang et al., 2003) |
|         | 21 | Epicatechin glucose               | C_{16}H_{18}O_{12} | /                        | Flavonoids             | (Zhou et al., 2011) |
|         | 22 | Kaempferol                        | C_{16}H_{18}O_{12} | 0.33                     | Flavonoids             | (Jiang et al., 2013) |
|         | 23 | Naringenin                       | C_{16}H_{18}O_{12} | 0.30                     | Flavonoids             | (Ma et al., 2014)   |
|         | 24 | Isolauriciresol                   | C_{30}H_{24}O_{12} | 0.60                     | Lignans                | (Jiang et al., 2013) |
|         | 25 | Methyl-3,4-dihydroxybenzoate      | C_{15}H_{18}O_{12} | 0.40                     | Phenolic acids         | (Jiang et al., 2013) |
| Pulps   |    | 2-[2-Hydroxy-5-(methoxycarbonyl)] phenoxoibenzoic acid | C_{12}H_{14}O_{6} | 1.68 | Phenolic acids | (Jiang et al., 2013) |
|         | 27 | Stigmastanol                      | C_{20}H_{30}O_{12} | 0.70                     | Sterols                | (Jiang et al., 2013) |
|         | 28 | Methylshikimate                   | C_{16}H_{20}O_{5} | 25.50                    | Esters                 | (Jiang et al., 2013) |
|         | 29 | Ethyl shikimate                   | C_{16}H_{20}O_{3} | 3.75                     | Esters                 | (Jiang et al., 2013) |
| Seeds   |    | Procyanidin A2                    | C_{21}H_{26}O_{12} | 0.18                     | Anthocyanins           | (Xu et al., 2010a)  |
|         | 8  | Proanthocyanidin A1               | C_{21}H_{26}O_{12} | 0.14                     | Anthocyanins           | (Xu et al., 2010a)  |
|         | 41 | Proanthocyanidin A6               | C_{21}H_{26}O_{12} | 0.19                     | Anthocyanins           | (Xu et al., 2010a)  |
|         | 42 | Aesculin tannin A                 | C_{17}H_{20}O_{18} | 0.26                     | Anthocyanins           | (Xu et al., 2010a)  |
|         | 43 | Litchitannin A1                   | C_{17}H_{20}O_{18} | 0.14                     | Anthocyanins           | (Xu et al., 2010a)  |
|         | 44 | Litchitannin A2                   | C_{17}H_{20}O_{18} | 0.18                     | Anthocyanins           | (Xu et al., 2010a)  |
|         | 45 | 2α,3α-Epoxy-5,7,3',4'-tetrahydroxyflavan-(4β–8)-catechin | C_{23}H_{28}O_{12} | 2.40 | Anthocyanins | (Wang et al., 2011a) |
|         | 46 | Epicatechin-(2β–O–7,4β–8)-epicatechin | C_{23}H_{28}O_{12} | 0.29 | Anthocyanins | (Xu et al., 2010b)  |
|         | 47 | 2β,3β-Epoxy-5,7,3',4'-tetrahydroxyflavan-(4κ–8)-epicatechin | C_{23}H_{28}O_{12} | 1.07 | Anthocyanins | (Wang et al., 2011a) |
|         | 48 | 2α,3α-Epoxy-5,7,3',4'-tetrahydroxyflavan-(4β–8)-epicatechin | C_{23}H_{28}O_{12} | 3.52 | Anthocyanins | (Wang et al., 2011a) |
|         | 49 | Litchiol A                        | C_{21}H_{20}O_{10} | 0.37                     | Anthocyanins           | (Wang et al., 2011a) |

(Continued)
| Parts No | Ingredients | Formula | Compound yield (mg/100g) | Category | Ref |
|----------|-------------|---------|---------------------------|----------|-----|
| 50 | Litchiol B | C_{12}H_{22}O_{9} | 0.07 | Anthocyanins | (Wang et al., 2011a) |
| 51 | (-)-Epicatechin-3-gallate (ECG) | C_{15}H_{14}O_{6} | 27.76 | Flavonoids | (Wen et al., 2014a) |
| 52 | Epicatechin-(7,8-bc)-4β-(4hydroxyphenyl)-dihydro-2(3H)-pyranone | C_{22}H_{18}O_{4} | 0.09 | Anthocyanins | (Xu et al., 2010b) |
| 53 | Quercetin | C_{15}H_{10}O_{7} | 0.13 | Flavonoids | (Xu et al., 2010a) |
| 54 | Pinocembrin-7-O-[6``-O-L-rhamnopyranosyl]-β-D-glucopyranoside | C_{31}H_{52}O_{10} | 0.16 | | |
| 55 | (-)-Pinocembrin-7-O-neohesperidoside (Onychin) | C_{27}H_{32}O_{13} | 0.69 | | |
| 56 | Kaempferol-7-O-neohesperidoside | C_{27}H_{30}O_{15} | 0.13 | Flavonoids | (Xu et al., 2010a) |
| 57 | Tamarixetin 3-O-rutinoside | C_{28}H_{32}O_{16} | 0.39 | | |
| 58 | Kaempferol-7-O-β-D-glucopyranoside | C_{21}H_{20}O_{11} | 0.07 | Flavonoids | (Wang et al., 2011a) |
| 59 | Pinocembrin-7-O-glucose | C_{21}H_{22}O_{8} | 0.23 | Lignans | (Xu et al., 2010a) |
| 60 | (2S)-Pinocembrin-7-O-(6``-O-L-rhamnopyranosyl)-β-D-glucopyranoside | C_{27}H_{32}O_{13} | 0.03 | Flavonoids | (Ren et al., 2011) |
| 61 | Naringin | C_{27}H_{32}O_{14} | 3.80 | Flavonoids | (Jiang et al., 2013) |
| 62 | (-)-Pinocembrin 7-O-rutinoside | C_{27}H_{32}O_{13} | 0.15 | | |
| 63 | Cinnamtannin B1 | C_{45}H_{36}O_{18} | 1.18 | Anthocyanins | (Wen et al., 2015) |
| 64 | (-)-Epicatechin (EC) | C_{15}H_{14}O_{6} | 27.76 | | |
| 65 | Luteolin | C_{15}H_{10}O_{7} | 0.10 | Flavonoids | (Wen et al., 2014a) |
| 66 | Kaempferol-3-O-β-D-glucoside | C_{21}H_{20}O_{11} | 9.41 | Flavonoids | (Wen et al., 2014a) |
| 67 | Pterodontriol-D-6-O-D-glucopyranoside | C_{21}H_{38}O_{18} | 0.20 | Flavonoids | (Wang et al., 2011a) |
| 68 | Taxifolin-4``-O-β-D-glucopyranoside | C_{27}H_{30}O_{16} | 0.88 | Flavonoids | (Tu et al., 2002) |
| 69 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |
| 70 | Protopaucic acid (PA) | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 71 | Scopoletin | C_{10}H_{8}O_{4} | 0.07 | Coumarins | (Wang et al., 2011a) |
| 72 | Butylated hydroxytoluene | C_{14}H_{22}O_{3} | 3.80 | Phenolic acids | (Prasad et al., 2009) |
| 73 | Gallic acid | C_{14}H_{22}O_{3} | 0.20 | Phenolic acids | (Prasad et al., 2009) |
| 74 | 2,5-Dihydroxy-hexanoic acid | C_{6}H_{12}O_{4} | 0.10 | Phenolic acids | (Wang et al., 2011a) |
| 75 | Cyclolitchtocotrienol A | C_{27}H_{40}O_{4} | 0.20 | | |
| 76 | Litchioside A | C_{17}H_{30}O_{10} | 0.23 | Lignans | (Xu et al., 2011) |
| 77 | Litchioside B | C_{20}H_{44}O_{10} | 0.10 | Lignans | (Xu et al., 2010a) |
| 78 | Pinuslongaeva A | C_{21}H_{38}O_{8} | 0.09 | Lignans | (Xu et al., 2010a) |
| 79 | Pinuslongaeva B | C_{21}H_{38}O_{8} | 0.16 | Lignans | (Xu et al., 2010a) |
| 80 | Pseudotriacetylgallate | C_{34}H_{42}O_{18} | 0.20 | Lignans | (Wang et al., 2011a) |
| 81 | Phlorizin | C_{14}H_{24}O_{10} | 0.60 | Fatty Acids | (Xu et al., 2011) |
| 82 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Tu et al., 2002) |
| 83 | Triterpenes | C_{45}H_{36}O_{18} | 1.18 | Flavonoids | (Xu et al., 2010a) |
| 84 | 2,5-Dihydroxy-hexanoic acid | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 85 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |
| 86 | 2,5-Dihydroxy-hexanoic acid | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 87 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |
| 88 | 2,5-Dihydroxy-hexanoic acid | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 89 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |
| 90 | 2,5-Dihydroxy-hexanoic acid | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 91 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |
| 92 | 2,5-Dihydroxy-hexanoic acid | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 93 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |
| 94 | 2,5-Dihydroxy-hexanoic acid | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 95 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |
| 96 | 2,5-Dihydroxy-hexanoic acid | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 97 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |
| 98 | 2,5-Dihydroxy-hexanoic acid | C_{14}H_{24}O_{5} | 0.43 | Phenolic acids | (Wang et al., 2011a) |
| 99 | 3-Oxotrirucalla-7,24-dien-21-oic acid | C_{30}H_{46}O_{3} | 0.88 | Fatty Acids | (Stuart and Buist, 2004) |

(Continued)
targets showed that 15 signaling pathways were involved in the chemotherapy and radiotherapy sensitization (Figure 4C and Table S9). All of the top 3 targets were elements of Amyotrophic lateral sclerosis (ALS), Colorectal cancer, Apoptosis, Hepatitis B, Tuberculosis and pathways in cancer, and 2 out of the top 3 targets were elements of p53 signaling pathway, Toxoplasmosis, Sphingolipid, and Neurotrophin signaling pathway, which indicates that the 10 pathways mentioned above might be responsible for the anticancer effect of Litchi on chemotherapy and radiotherapy sensitization (Figure 4D).

Other Anticancer Effects
Apart from the four effects exerted by Litchi ingredients for the major anticancer functions as listed above, several other targets were also found to be involved in the suppression of cancer stemness, metabolism, and angiogenesis, while also in the enhancement of immunity as listed in Table S10. However, the experiments validations on the anticancer effect of Litchi ingredients from these four aspects were very limited. Therefore, we only constructed a simple ingredient-target network map (Figure 5). The results showed that these mechanisms involved a total of 10 active ingredients, among which 5 belonged to the top ingredients from the previous screening including betulinic acid, EGCG, luteolin, gallic acid, and kaempferol, which further illustrated their importance. At the same time, we suggest that the remaining 5 ingredients (chlorogenic acid, (-)-Epicatechin-3-gallate (ECG), naringenin, cyanidin-3-glucoside, lupeol) and their detailed mechanisms need to be further explored.

DISCUSSION
Numerous studies have shown that Litchi contains a variety of anti-cancer ingredients, which act by multiple targeting. Emanuele and Ibrahim described Litchi’s nutritional value and reviewed the anti-tumor components and targets of Litchi with detailed listing but lacked a systematic analysis (Ibrahim and Mohamed, 2015; Emanuele et al., 2017). In the present study, we collected 110 compounds isolated from Litchi and found 19 components with anticancer effects based on 241 published research papers. The detailed information for each one of these compounds was listed in Tables 1 and 2 with corresponding targets. Then the network pharmacology approach was applied to explore the complicated “multi-ingredients, multi-targets, multi-pathways” anticancer mechanisms of Litchi from a system biology perspective.

We identified the top ingredients, top targets, and top signaling pathways of Litchi with anticancer effect from four major aspects including anti-proliferation, cell death promotion, inhibition of metastasis, and sensitization of chemotherapy and radiotherapy. Further, in order to identify the primary ingredients and targets acting on all four anticancer functions listed above, we performed analysis (Figure 6 and Table S11) and found EGCG and gallic acid to be the top ingredients participating in all of the four anticancer functions (Figure 6A and Table S11). Moreover, EGCG was also involved in the suppression of cancer stemness, cancer metabolism, and angiogenesis, while gallic acid was involved in attenuating angiogenesis (Table S10). These results suggest that they are likely to be the major anticancer ingredients in Litchi. Apart from that, we also found that kaempferol, luteolin, and betulinic acid were the top ingredients which carried out at least 2 of anticancer mechanisms (Figure 6A and Table S11). After selecting the primary ingredients from the overlapping parts, we found that BAX, BCL2, and CASP3 were the common targets which could induce apoptosis, autophagy, and sensitization, while AKT1 was a common target to suppress proliferation and induce apoptosis (Figure 6B and Table S11). To further study the interactions among top ingredients (EGCG and gallic acid) and top targets (BAX, BCL2, CASP3, and AKT1), a molecular docking study was carried out to elucidate their binding modes. The result indicated a high binding affinity between EGCG and 4 targets with all of their total score greater than 6. However, gallic acid showed a lower binding affinity with each of their total score less than 6, while only 2 top targets had active binding pockets for gallic acid.
| Category | Ingredients | Effects | Targets | Cancer types | Ref |
|----------|-------------|---------|---------|--------------|-----|
| Anthocyanins | | | | | |
| (-)-Epicatechin-3-gallate (ECG) | | anti-proliferation | | | |
| | | | | | |
| (-)-Epigallocatechin (EGC) | | promoting apoptosis | | | |
| | | | | | |
| (-)-Epigallocatechin gallate (EGCG) | | anti-proliferation | | | |
| | | | | | |
| Proanthocyanidins | B2 | | | | |
| Cyanidin-3-glucoside | | anti-proliferation | | | |
| | | attenuating angiogenesis | | | |
| | | inhibiting metastasis | | | |
| | | | | | |
| Cyanidin-3-rutinoside | (+)-Catechin | | | | |
| Flavonoids | | promoting apoptosis | | | |
| | | inhibiting metastasis | | | |
| | | | | | |
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(Continued)
TABLE 2 | Continued

| Category                      | Ingredients                                                                 | Effects                                                                 | Targets                                                                 | Cancer types                                           | Ref                                                                 |
|-------------------------------|-----------------------------------------------------------------------------|--------------------------------------------------------------------------|------------------------------------------------------------------------|--------------------------------------------------------|----------------------------------------------------------------------|
| sensitizing radiotherapy and  | CHEK2, CDKN1A, CASP3, GADD45A, DDIT3                                        |                                                                          | pancreatic, lung, cancer, and glioblastoma                           | (Saha et al., 2010; Elbaz et al., 2014)                 |                                                                      |
| chemotherapy                  |                                                                             |                                                                          |                                                                        |                                                        |                                                                      |
| Kaempferol                    | anti-proliferation                                                          |                                                                          |                                                                         |                                                        |                                                                      |
|                               | AKT1, CCNA/B1/D1/E, CDC2/25C, CDK1/2/20/45/1, CDKN1A, CHEK1/2, CMET, DNMT3B, ERBB3, ERRA, ERRG, GTF2H2, HIF1A, IF1/1R, MAP1LC3A, MAPK1/4/3, MCL1, MIR21/340, MTOR, PIK3CA/R1, PRKAA2, PTEN, SQSTM1, TP53, USF2 | bladder, breast, cervical, lung, colon, gastric, and liver cancer       | (Choi and Ahn, 2008; Li et al., 2009; Mylonis et al., 2010; Wang et al., 2013; Cho and Park, 2015; Huang et al., 2013; Lee et al., 2014a; Dang et al., 2015; Kim et al., 2016; Qiu et al., 2017; Drouet et al., 2018; Han et al., 2018a; Wu et al., 2018; Zhu et al., 2018; Zhang and Ma, 2019) |                                                                      |
| attenuating angiogenesis       | AKT1, ESRR, HIF1A, VEGFA                                                    |                                                                          | ovarian cancer                                                         | (Luo et al., 2009)                                     |                                                                      |
| inhibiting metastasis         | AKT1, CDH1/2, CULN, MAPK2/3, MIR21, MMP2/9, MTOR, MYC, PIK3CA, PTEN, PTK2, RAC1, RHOA, SNA,3, SNA1/1, VIM |                                                                         | breast, oral, cervical, lung, and renal carcinoma                      | (Lin et al., 2013; Jo et al., 2015)                    | (Lee et al., 2017a; Hung et al., 2017; Zhu et al., 2018)              |
| promoting apoptosis and       | AKT1, ATG7, ATM, BAD, BAX, BCL2/1, BECN1, BID, BIK, CASP3/7/8/9, CFLIP, CYC, DDI3, EHMT2, EREG, ERN1, FAS, H2AX, JNK, LC3/III, MAP2K1/2, MAPK1/3, MTCO2, TERT, TNFRSF10A | bladder, breast, cervical, colon, colorectal, endometrial, gastric, lung, and ovarian cancer |                                                        | (Nguyen et al., 2003; Li et al., 2009; Luo et al., 2011; Xie et al., 2013; Lee et al., 2014b; Kim et al., 2016; Yi et al., 2016; Kashafi et al., 2017; Zhao et al., 2017; Choi et al., 2018; Chuwa et al., 2018; Kim et al., 2018; Zhu et al., 2018; Zhang and Ma, 2019) |                                                                      |
| autophagy                      |                                                                            |                                                                          |                                                                        |                                                        |                                                                      |
| sensitizing chemotherapy      | ABC60, AKT1, BAX, BCL2/1, BIRC5, CASP3/7/8/9/10, CDKN1A, FAS, JAK1, JNK, MAPK1/14, MYC, NFKB, PARP1, PIK3CA, ROS1, STAT3, TNFRSF10A, XIAP | ovarian, lung, and colorectal cancer                                      |                                                        | (Luo et al., 2010; Kuo et al., 2015; Riahi-Chebbi et al., 2019) |                                                                      |
| Luteolin                      | enhancing immunity                                                          |                                                                          | breast cancer                                                          | (Azevedo et al., 2015)                                  | (Bandypadhyay et al., 2008)                                 |
| attenuating angiogenesis       | SLC2A1/16A1, CSF2, MAP2K1, MAPK2/3, PKC, PLC NOTCH1, VEGFA                  |                                                                          | gastric pancreatogenous, breast, lung, and colorectal cancer            | (Zhang et al., 2015a)                                  |                                                                      |
| inhibiting metastasis         | AIF, AKT1, ANO1, AURKB, BANF1, BAX, BCL2/1, BIRC5, CASP3/9, CCND1/1, CDKN1A, DEDD2, ENG, GAK, HSP90, HTERT, MAPK1/14/3, MCL1, MCL4, MIR107/1/30/21/224/301/34/3/42/570/380, MTOR, MYC, NFE2L2, NFKB, NOTCH1, PIK3CA, PTN, SNA1/2/3, STAT3, STAT1, STAT5, TEND1, TP53, VRK1 | breast, colon, gastric, lung, pancreatic, and prostate cancer |                                                        | (Chen et al., 2013; Huang et al., 2015b; Lin et al., 2017; Zang et al., 2017b; Yao et al., 2019) |                                                                      |
| promoting apoptosis           |                                                                            |                                                                          |                                                                        |                                                        |                                                                      |
| sensitizing chemotherapy      | BAX, BCL2/1, CASP3/7/8/9, CCNE2, CDH2, FAS, GSTA1/2, HMOX1, JAK1, JNK, MAPK1/14, NFE2L2, NFKB, PARP1, PPARG, PRKAR2A, PTK2, PTEN, RAC1, RELA, ROS1, SLC2A2, SNA1/2, STAT1/2/3, TWIST1, TYK2, VIM | ovarian, lung, colorectal, cervical, breast, ovarian, and liver cancer   |                                                        | (Tu et al., 2013; Chian et al., 2014; Qu et al., 2014; Tai et al., 2014; Yang et al., 2014; Cho et al., 2015; Dia and Pangilini, 2017; Wang et al., 2018a; Liu et al., 2018) |                                                                      |
| suppressing stemness          | BM1, COND1, CD44, FZD6, IL6, MYC, OCT4, PROM1, STAT3                         |                                                                          | prostate and oral cancer                                               | (Tu et al., 2016; Han et al., 2018b)                  |                                                                      |
| Naringenin                    | anti-proliferation                                                          |                                                                          | cervical, colon, colorectal cancer, and hepatocarcinoma                | (Totta et al., 2004; Song et al., 2015; Zhang et al., 2016) |                                                                      |
|                               |                                                                            |                                                                          |                                                                        |                                                        |                                                                      |

(Continued)
| Category | Ingredients | Effects | Targets | Cancer types | Ref |
|----------|-------------|---------|---------|--------------|-----|
| **inhibiting metastasis** | AKT1, CDH1, MAPK1/4, MMP2/9, NCL, NKFB, PKCZ, PKCE, RAC1, RH0, RH0A, SCN9A, SNAL1/2, TGFβ1, TWIST1, VIM | prostate, pancreatic, colon, breast, and gastric cancer | lung and pancreatic cancer | (Liao et al., 2014; Zhang et al., 2016; Chang et al., 2017; Aktas and Akgun, 2018; Han et al., 2018c; Zhao et al., 2019b) |
| **promoting apoptosis** | AKT1, MAP3K5, ATF3, BAX, BCL2, BIRC5, CASP3/8, JNK, MAPK1/3/14, TP53, RPS6KB1, ROS1, RPS6 | breast, prostate, and ovarian cancer | lung cancer and melanoma | (Li et al., 2013; Raha et al., 2015; Yoshinaga et al., 2016; Chen et al., 2018a) |
| **sensitizing chemotherapy** | CDKN2A, BCL2, CASP3/9, BAX, PTK2, MAPK14 | bladder, prostate, renal carcinoma, and breast cancer | lung cancer and melanoma | (Li et al., 2013; Raha et al., 2015; Yoshinaga et al., 2016; Chen et al., 2018a) |
| **enhancing immunity** | G2MB, ID2, IFNG, IRF2, SMA3/7 | breast cancer | lung cancer and melanoma | (Li et al., 2013; Raha et al., 2015; Yoshinaga et al., 2016; Chen et al., 2018a) |
| **Naringin** | AKT1, BIROC5, CDKN1A, CTNNB1, EGFR, MAPK1, MIR126, NKFB, PIK3CA, VCAN1 | breast and ovarian cancer | lung, cervical, gastric, and breast cancer | (Liu et al., 2013; Raha et al., 2015; Yoshinaga et al., 2016; Chen et al., 2018a) |
| **promoting apoptosis** | BAX, BCL2, CASP3/8/9, GSK3B, iKB, CHUK, MK2, NKFB, MAPK14, TP53, PARP1, TNF | colon and lung cancer | cervical and ovarian cancer | (Liu et al., 2013; Raha et al., 2015; Yoshinaga et al., 2016; Chen et al., 2018a) |
| **sensitizing chemotherapy** | PGP, ABCG2 | breast cancer | breast cancer | (Iriti et al., 2017) |
| **Gallic acid** | AKT1, CCNA/B1/D1/D3/E, CDC2/25C, CDK1/2/4/6, CHEK1/2, CDKN2A/2B/1A/1B, MAPK1/8/14, PIK3CA, SKP2, BAX, BCL2, CASP3 | bladder, prostate, renal carcinoma, and breast cancer | lung cancer | (Hou et al., 2017) |
| **phenolic acids** | AKT1, CCNA/B1/D1/D3/E, CDC2/25C, CDK1/2/4/6, CHEK1/2, CDKN2A/2B/1A/1B, MAPK1/8/14, PIK3CA, SKP2, BAX, BCL2, CASP3 | bladder, prostate, renal carcinoma, and breast cancer | lung cancer | (Hou et al., 2017) |
| **promoting apoptosis** | AKT1, CCNA/B1/D1/D3/E, CDC2/25C, CDK1/2/4/6, CHEK1/2, CDKN2A/2B/1A/1B, MAPK1/8/14, PIK3CA, SKP2, BAX, BCL2, CASP3 | bladder, prostate, renal carcinoma, and breast cancer | lung cancer | (Hou et al., 2017) |
| **attenuating angiogenesis** | AKT1, CDC42, CHUK, CJun, EGFR, GRB2, IL6, MAPK3/1/2, JUN, MAPK2/3/14, MEKK3, MMP2/9, NFkB, PIK3CA, PKC, PTK2, RAC1, RAS, RELA, RH0A, RH0B, ROS1, SOS1, SRC, STAT3 | oral, prostate, bladder, breast, and gastric cancer | cervical and ovarian cancer | (He et al., 2016; Sales et al., 2018) |
| **Protocatechuic acid (PA)** | AKT1, APAF1, ATM, ATR, BAK1, BAX, BCL2/L1, BIK, BRCa1, CASP3/8/9, CKII, CYC, EREG, GSH, H2AX, JNK, MDC1, MMIT, MTOR, PARP1, PPKD,ROS1, PPS6KB1, TP53, XIAP | oral, prostate, pancreatic, cervical, lung, and esophageal cancer | oral, prostate, pancreatic, cervical, lung, and esophageal cancer | (Faried et al., 2007; Chen et al., 2009; You et al., 2010; Russell et al., 2012; Liu et al., 2012a; Lu et al., 2016; Lin and Chen, 2017) |
| **sensitizing chemotherapy** | APAF1, BAX, BCL2, CASP3, CCNA/B, CCND1, DABLO, EGFR, HIF1A, IL6, JAK1, MTCO2, MYC, NOS2, PARP1, ROS1, SRC, STAT3, TP53, VEGFA, XIAP | lung and cervical cancer | lung and cervical cancer | (Phan et al., 2016; Wang et al., 2016a; Aboreshab and Osama, 2019) |
| **Betulinic acid** | FGF2, JNK, MAPK3/1/4, NFkB1, PTK2, RELA | lung cancer | lung cancer | (Tsao et al., 2014) |
| **attenuating angiogenesis** | AKT1, CDC42, CJun, CXL8, FGF2, FN1, IL6, MMP2/9, NCL, NKFB/IA, PKCα, PKCE, RAC1, RAS, RH0A/B, USP2, VEGFA | lung and ovarian cancer | lung and ovarian cancer | (Tsao et al., 2014; Xie et al., 2018) |

(Continued)
with a total score of more than 5 (Figure 7 and Table S12). We speculated that gallic acid might exert anticancer effects by indirectly interacting with the top targets. Other than identifying single ingredient and its corresponding effect or vice versa, we mapped the complex interactive network of the primary targets and ingredients from Litchi (Table S11). The results could be used to maximize the effects of Litchi ingredients by extracting only the identified functional components based on the principles of Component Formula, which is a new model to develop innovative TCM with the understanding of the effective ingredients and pharmacological mechanisms (Zhang and Wang, 2005). Notably, we have also found that some of the top pathways screened out in this study have been experimentally verified, such as PI3K-Akt, Ras and MAPK signaling pathways etc. (Lin et al., 2011; Wang et al., 2011a; Lim et al., 2017). Hence, we have collected and summarized the results from independent studies, and also investigated further into the complex network of the multiple active ingredients and targets of Litchi. This would help to guide people to further explore the potential cancer therapy values of Litchi.

TABLE 2 | Continued

| Category | Ingredients | Effects | Targets | Cancer types | Ref |
|----------|-------------|---------|---------|--------------|-----|
| promoting apoptosis | AKT1, BAD, BAX, BCL2, CDH1, CASP3/9, CYC, NFKB1, CHUK, MKI67, PMAIP1, CDKN1A/1B, TP53, CTKL2, PARP1, PIK3CA, ROS1, TIMP2, XIAP | colon, gastric, colorectal, cervical, prostate, and pancreatic cancer | (Shankar et al., 2017; Zeng et al., 2019) |
| sensitizing chemotherapy | BAX, BCL2, BIRC5, CASP12/3, CDK6, CTNNB1, DDIT3, EGFR, ERF2A, GSK3B, HK2, HSPA5, MAP1LC3B, MAPK1, PARP1, RB1, SQSTM1, STAT3, TIM8, VDAC1 | breast and lung cancer | (Ko et al., 2018; Cai et al., 2018; Wang et al., 2019c) |
| inhibiting metabolism | CAV1, IKB, LDHA/B, MYC, PK1, RELA | breast cancer | (Jiao et al., 2019; Zeng et al., 2019) |
| suppressing stemness | NANOG, OCT4, PRKAA2, SOX2 | pancreatic cancer | (Sun et al., 2019) |
| sensitizing promoting apoptosis | AKT1, GSK3B, RELA, BAX, BCL2, SNAIL1, VIM | pancreatic cancer | (Zhang et al., 2009) |
| sensitizing chemotherapy | BCL2, CLAUDIN1, MMP2/9, MTCO2, NFKB, RELA, TP53 | colorectal and breast cancer | (Wang et al., 2016b; Wang et al., 2018c) |
| promoting apoptosis | APAF1, BAX, BCL2, CASP3/9, EGFR, MKI67, PARP1, PCIN | cervical, head and neck, lung, and prostate cancer | (Prasad et al., 2008; Bhattacharyya et al., 2017; Min et al., 2019) |
| sensitizing chemotherapy | ABCG2, MAPK1, EIF2A, CASP3 | colorectal cancer | (Chen et al., 2018b) |
| enhancing immunity | AKT1, BCL2, CLAUDIN1, IFNG, LAMP1, MAPK2/3, PIK3CA, PRF1 | gastric cancer | (Wu et al., 2013) |
This study systematically explored the anti-cancer mechanisms of Litchi using network pharmacology methods. However, it was distinct from traditional network pharmacology research, in which, the components and targets of a natural herb were mainly predicted based on online databases, followed by experimental verification in vitro and in vivo. In contrast, in this study, experiments were not of necessity because the anti-cancer ingredients, targets, and their interactions have already been experimentally confirmed in published literature. Furthermore, we collected information from independent studies and transformed them into a systematic interaction network with further analysis of the top ingredients, top targets and possible signaling pathways. For the first time, the anti-cancer properties of Litchi were explored from a new “multi-ingredients, multi-targets, and multi-pathways” perspective. However, selecting the top ingredients and top targets by network pharmacological methods alone has limitations, such as that it could neither reflect the anticancer effect intensity of these top ingredients, nor indicate if there was a correlation between the effectiveness of the ingredients and their concentrations. Also, we could not compare the pharmacokinetic parameters which directly affect drug efficacy. Therefore, based on the results of this article, we would use these top ingredients as a “Component Formula” in a combinatory manner and to explore their anti-cancer effect with in vitro and in vivo experiments in the follow-up studies.

DATA AVAILABILITY STATEMENT

All datasets generated for this study are included in the article/Supplementary Material.

AUTHOR CONTRIBUTIONS

HG, SC, and ZS designed this work. SC, YH, and YC drafted the manuscript. HG, YH, and DZ performed the network pharmacology analysis. QL made the figures. All authors read and approved the final version.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphar.2020.00451/full#supplementary-material

ABBREVIATIONS

See Table S13.
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**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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