Abstract: Discovery of microRNAs (miRNAs) twenty years ago, has advocated a new era of “Molecular Genetics”. About 2000 miRNAs are present, that regulate one third of the genome. MiRNAs dysregulated expression may contribute to several diseases including tumor growth. Their presence in body fluids, reflecting levels alteration in various cancers, merit circulating miRNAs as the “next generation biomarkers” for early stages tumor diagnosis and/or prognosis. Herein, we performed a comprehensive literature search focusing on the origin, biosynthesis and role of miRNAs and summarized the foremost studies centering on miRs value as non-invasive biomarkers in different non-communicable diseases, including various cancer types. Moreover, during chemotherapy many miRNAs were linked to multidrug resistance, via modulating numerous biological processes and/or pathways that will be highlighted as well.

Keywords: ncRNA; miR; NCDs; onco-miR; cancer; mTOR
non-invasive identification of various cancer types[10][11][12][13] considered as beneficial potential liquid biopsy.

2. Review Aims

2.1. In Part I, the review aims to briefly discuss “miRs biosynthetic pathways and down-stream effects upon binding target mRNA”.

2.2. In Part II, the review aims to highlight “the utility of circulating miRNAs as biomarkers for non-communicable diseases (NCDs) and a brief about their role in cancer growth or resistance to treatment”.

3. Review Methodology

An online search in the medical databases PUBMED and NCBI for the following terms: (“Circulating miRNA”) AND (“Health and diseases regulation of gene expression”) AND (“Role in Carcinogenesis”) AND (“Epigenetics”) AND (“Future promising biomarkers”) was done on September, 2020, with publication date limit since 2015. Priority was given to papers with higher empirical evidence methodology, including clinical guidelines, meta-analysis, randomized clinical studies, systematic review, original papers, and narrative reviews.

Part I.

4. MiRNAs Biogeny

MiRNAs biogenesis include various coordinated steps and specific cellular mechanisms[8]. Biogenesis of miRNA starts with post-transcriptional or co-transcriptional preparation of RNA polymerase II-III transcripts. Around 50% of the miRNAs recently identified are intragenic and are typically regulated from introns and some protein-coding gene exons. The remaining ones are intergenic, freely transcribed and guided according to their own promoters from a host gene[14]. MiRNAs could be translated as a single long transcript, named clusters[15]. Moreover, miRNAs biogenesis is categorized as either canonical or non-canonical.

4.1. Canonical miRNAs Biogeny Pathway

This is the main route by which miRNAs are developed, as shown in Figure (1). In this process, primary-miRNAs (pri-miRNAs) are transcribed from their genes by RNA polymerase II. Which is then handled by a microprocessor complex composed of DiGeorge Syndrome Critical Region 8 (DGCR8); an RNA-binding protein, Drosha, a Class 2 ribonuclease III enzyme into precursor-miRNAs (pre-miRNAs)[16]. In this process, DGCR8 identifies an N6-methyl adenylated GGAC and a different motif within the pri-miRNA[16], while Drosha begins processing inside the nucleus by cutting the stem-loop precursor[17].

For most of the double stranded RNAs (dsRNAs) which are involved in small-RNA production routes, pre-miRNA seems to be a signature motif. This signature is recognized by the Exportin-5 protein; that facilitates the release of pre-miRNAs to the cytoplasm, through nuclear pores, depending on a GTP-GDP gradient[17]. Exported pre-miRNA is transferred to another RNase-III enzyme in the cytoplasm, called Dicer. Dicer, the cytoplasmic RNase-III enzyme, cuts the pre-miRNA to a miRNA duplex, which is unwinded afterwards giving the “Fully Developed Functional miRNA” molecule.

In an ATP-dependent manner, the two strands defined from the resultant miRNA duplex, might be stacked into the protein family Argonaute (AGO) known as AGO1-4[18]. After miRNA duplex formation, one strand of the miRNA associates with an RNA-induced silencing complex (RISC) forming the “regulatory miRNA-RISC complex”. The choice of strands 5p or 3p is dependent on the thermodynamic stability at the 5’ untranslated regions (UTRs) at the 1-position of the nucleotide[19]. The unoccupied strand known as the
passenger strand is loosened by different components from the loaded strand, named the guide or leading strand, depending on complementarity[6].

![Figure 1: Canonical miRNAs Biogeny Pathway](image)

Figure 1: Canonical miRNAs Biogeny Pathway

[It is the primary route by which miRNAs are produced. In the nucleus, the gene is transcribed to generate primary miRNA (pri-miRNA) that is cleaved producing precursor miRNA (pre-miRNA), which is then exported to the cytoplasm to be broken, resulting in miRNA duplex. miRNA duplex links to RISC complex resulting in miRNA duplex unwinding to create a mature miRNA. Every mature miRNA binds to its target mRNA, resulting in silencing by cleavage, de-adenylation or repressing translation.]

4.2. Non-Canonical miRNAs Biogenic Pathway

Several non-canonical pathways have been illustrated to date, primarily Drosha/DGCR8-independent and dicer-independent pathways[6].

4.2.1. Drosha/DGCR8-Independent Non-Canonical MiRNAs Pathway

This pathway joins mRNA introns and their own transients to “mirtrons transcripts”. Drosha/DGCR8 is skipped at that stage of processing and these transcripts are, again, carried by the protein Exportin-1 to the cytoplasm[17].

4.2.2. Dicer-Independent miRNAs Biogenic Pathway

mRNAs could be dealt by Drosha/DGCR8 to form short heterogeneous RNA (shRNA). Since these transcripts are not lengthy to serve as dicer substrates, AGO2 protein leads in their cytoplasmic developmental steps[20], as previously mentioned.
5. **MiRNAs-Target Binding**

Via complementarity between unique sequences, which are 2-7 bases, from the 5' end of the miRNA and certain target mRNA sequences, recognized as "**miRNA Response Elements**" (MREs), the developed miRNA attaches to its target[21].

5.2. **MiRNA-Target Gene mRNA-Binding Types**

5.2.1. **Ideal Binding** where complete complementarity occurs when miRNA binds its target ORF resulting in an "**RNA Decay**" or

5.2.2. **Imperfect Binding** resulting in "**Post-Transcriptional Silencing**" via mRNA de-stabilization, de-capping, de-adenylation and translational repression[6],[22].

It is worthy to mention the fundamental multifaced aspect of miRNAs target binding, is that their suppressive role is not limited to one-mRNA, highlighting the "**One-mRNA Paradigm**" in which multiple mRNA targets can be achieved by one microRNA and multiple microRNAs can hit one mRNA[23].

5.3. **MiRNA-Target Gene(s) mRNA Silencing Mode(s)**

Depending on the degree of MREs complementarity, the target gene(s) mRNA silencing strategies, by miRNAs, could be attained either via target gene mRNA degradation or target gene mRNA translation repression.

5.3.1. **Target mRNA Decay**

MiRNA-induced silencing complex (miRISC) AGO proteins bind to the GW182 (a protein-containing glycine-tryptophan repeat) to enroll the “de-adenylase complex” and promote de-adenylation of the target gene mRNA poly(A) tail. With the aid of the catalytic de-capping protein-2 (DCP2), after de-adenylation, and in the presence of an additional de-capping activators, miRISC de-caps the de-adenylated gene mRNAs. In the presence of an enhancer of de-capping 4 (EDC4), DCP1 and additional de-capping cofactors, the decay of the target mRNA is aided by the cytoplasmic 5' to 3' exonuclease1 (Xrn1p)[24].

5.3.2. **Target mRNA Translation Repression**

miRNA-mediated target mRNA translational repression can occur before and after translational initiation step, through several mechanisms.

5.3.2.1. **miRISC ties to the target mRNA** at that point AGO protein interacts with the GW182. This interaction promotes the relocation of poly(A) binding protein from the 3’ poly(A)-tail and blocks its binding to the eukaryotic initiation factor 4 complex (eIF4G), interfering with the “translation-initiation step”[25].

5.3.2.2. **Repressing cap-structure recognition by eIF4F complex** where the AGO protein separates the eIF4A from the 5’ cap binding complex of the target mRNA and therefore, the ribosomal subunit will not be recruited or attached to the mRNA for translation initiation[25].

5.3.2.3. **miRNA can repress protein synthesis** after target mRNA translation initiation.

5.3.2.4. Additionally, miRISC could interferes with the targeted mRNA **elongation components**[25].

5.3.2.5. Finally, to ensure no escape from miR silencing effect, if the target mRNA was translated, miR-ISC could recruit **proteases** resulting in degradation of the nascent polypeptide chains[25].
5.4. MiRNA-Target Gene(s) Activation Mode

Activated targeted mRNA expression could be triggered by miRNAs[6], via AGO2 protein and fragile-x-mental retardation related protein-1, rather than GW182. This is achieved via MiR attachment on the target promoter, to induce RNA-Polymerase II recruitment followed by transcription activation[26]. Either “MiR-target gene(s) binding” resulted in an expression silencing or activation, these effects have been witnessed and recorded by researchers to be associated with various disease(s), that will be discussed in the current review Part II.

Part II.  
6. MiRNAs Expression Alterations in Non-Communicable Diseases

6.2. MiRNAs Relation to Glucose Homeostasis

MiRNAs Effect on Adipogenesis, Metabolic Syndrome or Weight Control[27] MiRNAs may boost or inhibit mesenchymal stem cell adipogenic differentiation (Table 1). MiRs establish adipocyte differentiation, through directing adipogenesis-related transcription components and signal transduction pathways[28]. This could be mediated via AKT/mTOR signaling pathway, with an effect on glucose homeostasis and adipogenesis increment, characterized by the final up-regulation of adipogenic markers[29]. On the other hand, miRNAs would repress adipogenic differentiation via adipogenic factors down-regulation, together with a decreased triacylglycerol level[30].

6.2.1. MiRNAs Relation to Type 2 Diabetes Mellitus

As listed in Table 1, many miRNAs are linked to β-cells growth, insulin resistance or sensitivity, insulin production/secretion and insulin signaling, which can influence T2DM disease course[31]. Therefore, diabetes-related nephropathy or retinopathy is also affected by an altered microRNAs expression[32].

6.2.2. MiRNAs Lists in Cardiovascular Diseases

miRNAs regulate the cardiac progenitor cells differentiation and proliferation, controlling cardiac myocytes, endothelial cells, pacemaker cells, as well as smooth muscle cells function. Table 2 shows miRNAs lists dysregulated in various CVDs[33]. For example, miR-208a and miR-208b, encoded within alpha and beta-cardiac muscle myosin heavy chain genes, respectively, were found to be elevated in patients with acute myocardial infarction (AMI). Liu and his co-workers[34] demonstrated a significant predictive value for miR-208, miR-1 and miR-499 in AMI, higher than the traditional cardiac biomarkers, namely, TnT and CPK-MB.

6.3. MiRNAs List in Cerebrovascular Diseases

miRNAs are essential to the nervous system's improvement, with few miRNAs having function in developing ischemic cerebrovascular disorders incapacity[35]. Many miRNAs have been associated with post-stroke brain edema and post-stroke cell death, namely, apoptosis.[36]As listed in Table 3.

6.4. MiRNAs in the Oncology field

6.4.1. Onco-miR or Tumor Suppressor miR; a Coin with Two Faces

Being a multifactorial player, miRNA in the oncology field represents a coin with two faces, either oncogenic or tumor suppressor[37], as listed in Table 4. miRNAs that can hit/suppress various mediators of the oncogenic signaling pathways, is known as a tumor suppressor mediator[38][39][40]. On the contrary, the miRNA that aims the cell-cycle checkpoint proteins or the fundamental tumor suppressor proteins, is nominated the oncogenic miRNA or an onco-miR[41].
### Table 1: MiRNAs List in relation to Glucose Homeostasis; Adipogenesis, Metabolic Syndrome, and Type 2 D.M

| Metabolic Disease                  | miRNAs Effect                        | miRNAs List                                                                 |
|-----------------------------------|---------------------------------------|------------------------------------------------------------------------------|
| Obesity & Metabolic Syndrome      | Adipogenesis promoting                | miR-26b[42], miR-103[43], miR-146b, miR-148a[44], miR-199a, miR-181, miR-320[28] |
|                                   | Anti-adipogenic                       | miR-33b, miR-93[45], miR-125a, miR-193a/b[46], miR-194, miR-363, miR-709[27] |
| Type 2 D.M                        | ß-cells development                   | miR-197-3p, miR-9-5p, miR-9-3p, miR-99a-3p, miR-124a, miR-135a, miR-138, miR-149, miR-342-3p, miR-375, miR-106b, miR-222[47][48][49][50][51][52][53] |
|                                   | Insulin sensitivity/resistance        | miR-31, miR-127, miR-302c3p, miR-373, miR-518b, miR-520c-3p, miR-200, miR-7[54][55][56][57][51] |
|                                   | Insulin production/secretion          | miR-29, miR-221, miR-222, miR-103, miR-107, miR-223[58] miR-320, miR-126, miR-103, miR-107[59][31] Let-7 family[60] miR-375, miR-9, miR-7, miR-124a, miR-96, miR-124, miR-184, miR-29a[47][51] |
|                                   | Insulin signaling                     | miR-7, miR-1, miR-133a/b miR-206, miR-128a, miR-330, miR-223[61][62][63] miR-144 |

### Table 2: MiRNAs Lists associated with different Cardiovascular Diseases

| Cardiovascular Disease(s)         | miRNAs List                                                                                 |
|-----------------------------------|-----------------------------------------------------------------------------------------------|
| Acute Myocardial Infarction       | miR-208a/b, miR-1, miR-133a/b, miR-499[34], miR-328, miR-134, miR-1291, miR-663b, miR-22[64], miR-126[65] |
| Heart Failure                     | miR-423-5p, miR-22, miR-320a, miR-92b[33], miR-21[66]                                          |
| Atrial Fibrillation               | miR-133b, miR-328[20], miR-499[67], miR-126[68]                                               |
| Hypertension                      | miR-34a, miR-21[69], miR-23b, miR-191, miR-451, miR-126-3p, miR-26a-5p, miR-107[70]           |
| Cerebrovascular Disease(s) | miRNA Regulatory Effect | miRNAs List |
|---------------------------|-------------------------|-------------|
| Stroke                    | Up regulation           | miR-125b-2, miR-422a, miR-488, miR-627[71], miR-290[72], miR-124, miR-27a, miR-10a, miR-182, miR-200b[73], miR-298, miR-106b-5p, miR-4306[74] |
|                           | Down regulation         | let-7f, miR-126, miR-1259, miR-142-3p, miR-15b, miR-186, miR-519e, miR-768-5p[35], miR-320e, miR-320d[35] |
| Alzheimer’s               | Up regulation           | miR-146a[75], miR-361-5p, miR-30e-5p, miR-93-5p, miR-15a-5p, miR-143-3p, miR-106b-5p, miR-101-3p, miR-424-5p, miR-106a-5p, miR-18b-5p, miR-3065-5p, miR-20a-5p, miR-582-5p[76] |
|                           | Down regulation         | miR-31, miR-93, miR-143, miR-146a[75], miR-1306-5p, miR-342-3p, miR-15b-3p[76] |
| Parkinson’s               | Up regulation           | miR-331-5p[77], miR-137-3p, miR-124-3p[78], miR-30a/b-5p[79] |
|                           | Down regulation         | miR-29a/c-3p, miR-19a/b-3p[80] |
Table 4: miRNAs Lists associated with Various Types of Cancer and their effects either oncogenic or tumor suppressor

| Cancer Type | miRNA Role | miRNAs List |
|-------------|------------|-------------|
| Leukemia    | Oncogenic  | miR-128a, miR-128b, miR-150, miR-181b-5p, miR-423-3p, miR-486-5p, miR-92b-3p[81] |
|             | Tumor Suppressor | miR-15a, miR-16-1[82], miR-495 |
| Breast      | Oncogenic  | miR-128[83], miR-10b, miR-373[37], miR-520c, mir-21, mir-155 |
|             | Tumor Suppressor | mir-125a/b, miR-142[84], miR-124-3p[85], miR-101, miR-204-5p[86], miR-491-5p[87], miR-491-5p[87], miR-206[88], miR-152[89], miR-142-3p[90] |
| Gastric     | Oncogenic  | miR-23a[91], miR-27a[92], miR-223[93], miR-106a[94], miR-106b-25 cluster, miR-107[95] |
|             | Tumor Suppressor | miR-145, miR-143[96], miR-9[97], miR-34b[98], miR-124a, miR-335, miR-218, miR-484[99] |
| HCC         | Oncogenic  | miR-182-5p[100], miR-106b-3p, miR-101-3p, miR-1246[101], miR-221, miR-224 |
|             | Tumor Suppressor | miR-34a, miR-199a[102], miR-200a |
| Prostate    | Oncogenic  | miR-141 and miR-21[103], miR-125b[104] |
|             | Tumor Suppressor | miR-145, miR-143[105] |
| Pancreatic  | Oncogenic  | miR-132, miR-212, miR-122-5p, miR-125b-5p, miR-192-5p, miR-193b-3p, miR-221-3p, miR-27b-3p[106], miR-222[66], miR-181a/b/d[107], miR-155, miR-103, miR-107 |
|             | Tumor Suppressor | miR-125b-5p[106], miR-34a, miR-96, miR-221 |
| Ovarian     | Oncogenic  | miR-16, miR-939[108], miR-21, miR-27a, miR-26a/b, miR-103, miR-182, miR-223, miR-205[109], miR-206, miR-195, miR-10b, miR-7, miR-429[110] |
|             | Tumor Suppressor | miR-145, miR-125b, miR-211[111], miR-25, miR-377, miR-432, miR-124a, miR-436, miR-302a[112] |
| Uterine     | Oncogenic  | miR-15b[113] |
| Leioymoma   | Tumor Suppressor | miR-29a/b/c, miR-197, miR-200c[113] |
| Thyroid     | Oncogenic  | miR-129-1, miR-146b, mir-183, mir-197[114], miR-146b[115] |
|             | Tumor Suppressor | miR-338-3p[116], miR-497[117] |
| Colorectal  | Oncogenic  | miR-1246, miR-1308, miR135b-5p, miR-183-5p, miR-18a-5p, miR18b-5p, hsa-miR-21-5p, miR-223-3p, miR-224-5p, miR-503-5p[118] |
|             | Tumor Suppressor | miR-1-3p, miR-133b, miR-143-3p, miR145-5p, miR-150-5p, miR-195-5p, miR215-5p, miR-375, miR-378-3p, miR-497-5p[118] |
| Melanoma    | Oncogenic  | miR-195[119], miR-210[120] |
|             | Tumor Suppressor | miR-193a, miR-33a[121]miR-let-7b/c |
| Pituitary adenoma | Oncogenic | miR-128a, miR-155, miR-516a-3p, miR-372, miR-181b-5p, miR-181d, miR-191-3p, miR-598[122] |
|             | Tumor Suppressor | miR-34a[123], miR-3676-5p, miR-383[122] |
| Osteosarcoma | Oncogenic | miR-504[124], miR-149[125] |
| Neuroblasto ma | Oncogenic | miR-181a/b[126], miR-1268, miR-1303[127], miR-1308, miR-1908, miR-198, miR-513b-5p, miR-548h, miR-580 |
|             | Tumor Suppressor | miR-513, miR-548a/f-5p, miR-323-5p, miR-342[128], miR-639, miR-640, miR-641, miR-662, miR-34a[129], miR-16, miR-15a/b[130] |
| Lung non- small cell | Oncogenic | miR-25[131], miR-7, miR-34a, miR-328-3p[132], miR-499a[133] |
|             | Tumor Suppressor | miR-451[134], miR-214 |
| Bladder     | Oncogenic  | miR-222, miR-452, miR-6724-5p, miR-1185-1-3p, miR-6831-5p[135] |
|             | Tumor Suppressor | miR-143, miR-99a-5p[136], miR-6087, miR-3960, miR-1343-5p[135] |
| Cervical    | Oncogenic  | miR-31[137], miR-19a/b, miR-145[138],miR-155[139],miR-125a[140] |
|             | Tumor Suppressor | miR-34a[141], miR-886-5p[142] |

6.4.2. MiRNAs Involvement in Carcinogenesis via mTOR Signaling

In different types of cancer, the mechanistic target of rapamycin (mTOR); a conserved serine/threonine kinase enzyme involved in cell metabolism, could be hyperactive, leading to an abnormal cell proliferation
and eventually cancer[143]. An association was observed between miRNA(s) and the mTOR pathway during cancer growth[143].

6.4.2.1. mTOR Signaling Pathway link to miRNA Biogenesis

Targeted Raptor mutation, a fundamental component of mTORC1 type, may affect increments in miRNA biogenesis[144]. On the other hand, Mdm2-dependent ubiquitination of Drosha, an RNase assigned to pri-miRNA formation to give pre-miRNA, therefore, mTOR activation widely suppresses miRNA biogenesis[144]. Few specific miRNA(s)-related to cancer are known to be regulated by mTOR signaling, as sketched in Figure (2).

However, many miRNAs have been documented to target various mTOR signaling stages in different types of cancer, as shown listed in Table 5.

Figure 2: mTOR route Controls the Expression Levels of some miRNAs

[Through Mdm2-dependent pathway and Drosha decaying, mTOR governs some miRNAs synthesis.]
| miRNAs List | Targeted Gene(s) | Cancer Type | Effect |
|-------------|-----------------|-------------|--------|
| miR-7[145]  | AKT, PlK        | HCC         | Proliferation, Invasion |
| miR-99      | mTOR, AKT       | Endometrial, NSCLC, Cervical Breast Pancreatic HCC, Esophageal, Bladder | Proliferation, Invasion, Apoptosis, Cell Cycle, Autophagy, Tumor Formation |
| miR-101[143]| EZH2, mTOR      | HCC, Osteosarcoma | Proliferation, Invasion, Cell Cycle |
| miR-122[150]| PlK            | Breast      | Proliferation |
| miR-149[143]| mTOR, AKT      | Cervical Gioma, HCC | Proliferation |
| miR-193a-3p/5p[151][152][153]| mTOR, PlK | NSCLC | Proliferation, Migration, Epithelial Mesenchymal Transition (EMT) |
| miR-204[154]| mTOR           | NSCLC       | Metastasis |
| miR-155[143]| AKT, S6K1, Rictor | Cervical Nasopharyngeal Breast | Autophagy |
| miR-214[155][156]| AKT       | Renal       | Proliferation |
| miR-218[157][158][159]| PlK, AKT, mTOR | Colorectal OSCC, Cervical HCC | Tumorogenesis Progression, Invasion, Migration Metastasis |
| miR-125a[160]| mTOR         | Glioma, Endometrial HCC | Proliferation |
| miR-199a[161]| mTOR         | Glioma, Endometrial HCC | Proliferation |
| miR-22[162]| mTOR           | Suprarenal epithelioma | Metastasis |
| miR-93[163][164][165][166]| PTEN | Osteosarcomas, Ovarian Breast | Proliferation, Migration, Invasion, Inhibiting Apoptosis |
| miR-532-5p[167]| mTOR | Gastric | Proliferation, Metastasis |
| miR-451[168]| mTOR, AMPK    | Colon       | Proliferation, Migration |
| miR-205[169]| PTEN           | NSCLC       | Proliferation, Angiogenesis |
| miR-96[170][171][172]| mTOR, PRAS40 | Prostatic Breast Pancreatic | Proliferation, Metastasis |
| miR-634[173]| mTOR           | Cervical    | Proliferation, Metastasis, Apoptosis |
| miR-21      | TSC            | Gastric     | Proliferation, |
6.4.3. MiRNAs and Multidrug Resistance in Cancer Therapy

Over decades, the significant clinical obstacle to successful cancer treatment is multidrug resistance (MDR), arising from ATP binding cassette (ABC) drug transporter(s) dysregulation, apoptosis or autophagy machinery surrender, redox homeostasis imbalance, as well as drug dysregulated metabolism and drug target alterations[182]. Several manuscripts addressed miRNAs role in MDR[183][184][185] Therefore, miRNAs might be potential targets for preventing chemotherapy MDR. Differences in miRNAs expression pattern in drug-resistant cancer cells relative to drug-sensitive cells[182], have been reported. miRNAs list to regulate MDR by stressing on a specific cellular-signaling pathway or transporters is summarized in Table 6.

Table 6: miRNAs List involved in Multi Drug Resistance highlighting their regulatory function(s) and the MDR targets

| Regulation of Target | miRNAs List |
|----------------------|-------------|
| MDR Transporters     |             |
| ABCB1/MDR1           | miR-302c, miR-3664[186], miR-873[187], miR-381, miR-495, miR-223, miR-203a, miR-200c[188], miR-508-5p[189] |
| ABCG2/BCRP           | miR-328, miR-519, miR-520, miR-181a, miR-487a, miR-519c, miR-212[190] |
| ABCC1/MRP1           | miR-326, miR-1291, miR-508-5p[191] |
| p53                  | miR-125a/b, miR-140[192], miR-122, miR-34 |
| CDK6                 | miR-34a, miR-139-5p[193], miR-143[194], miR-503, miR-1271 |
| BCL2                 | miR-15b, miR-16, miR-21, miR-497, miR-200bc/429, miR-1915, miR-214, miR-195[195], miR-205 |
| BCL-XL               | miR-574-3p |
| MCL-1                | miR-101[196] |
| BIM                  | miR-494 |
| BAX                  | miR-365 |
| Caspase-3            | miR-30 b/c, miR-21 |
| PTEN                 | miR-21, miR-22, miR-221, miR-214, miR-19a/b, miRNA-17-5p, miR-222[197] |
7. Conclusion

7.1. One abundant class of ncRNAs is miRs. MiRs are involved in the pathogenesis as well as detection of various NCDs, including different cancer types. Moreover, miRNAs are linked to mTOR signaling pathway, a fundamental pathway of MDR and/or carcinogenesis. Current evidence indicates that in most diseases, including the NCDs, miRNAs and mTOR binding do happen.

7.2. Recommendations

Being ideal biomarkers for predicting chemotherapy response, miRs would be possible goals for future drug design to solve MDR. Additionally, combining miRNAs detection together with the mTOR signaling route components, being related to SNPs, would draw the complete picture concerning miRNAs as viable targets for evaluating and prognosticating NCDs.

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List of abbreviations

| Abbreviation | Full Form |
|--------------|-----------|
| ABCB1        | ATP Binding Cassette Subfamily B Member 1 |
| ABCC1        | ATP Binding Cassette Subfamily C Member 1 |
| ABCG         | ATP binding cassette super-family G member |
| AGO          | Argonaute |
| AMI          | Acute myocardial infarction |
| AMPK         | Adenosine-5-monophosphate-activated protein kinase |
| ATG5         | Autophagy related 5 |
| BCL-XL       | B-cell lymphoma-extra large |
| MRE          | MiRNA response elements |
| MRPI         | Multidrug resistance-associated protein 1 |
| mTOR         | Mechanistic target of rapamycin |
| NCDs         | Non communicable diseases |
| ncRNAs       | Noncoding RNAs |
| NSCLC        | Non small-cell lung carcinoma |
| ORF          | Open reading frame |
| OncomicR     | Oncogenic miRNA |
| Abbreviation | Full Form |
|-------------|-----------|
| BCL2        | B-cell lymphoma 2 |
| BCRP        | Breast cancer resistant protein |
| CDK6        | Cyclin-dependent kinase 6 |
| CRC         | Colorectal cancer |
| CYP         | Cytochrome P450 |
| CVD         | Cardiovascular diseases |
| DCP         | De-capping protein |
| DGCGR8      | Drosha-DiGeorge syndrome-critical region gene 8 |
| DPD         | Dihydropyrimidine dehydrogenase |
| dsRNA       | Double stranded RNAs |
| EDC4        | Enhancer of de-capping 4 |
| eIF4G       | Eukaryotic initiation factor 4 |
| ERK         | Extracellular signal-regulated kinase |
| GSH         | Glutathione |
| GST         | Glutathione S-transferases |
| HCC         | Hepatocellular carcinoma |
| MAPK        | Mitogen-activated protein kinase |
| MDR         | Multidrug resistance |
| miRNA       | MicroRNA |
| PD          | Parkinson’s Disease |
| PDCD4       | Proapoptotic factors programmed cell death 4 |
| PI3K        | Phosphoinositide 3- kinase |
| PPARγ       | Peroxisome Proliferator-activated Receptor γ |
| Pre-miRNAs  | Primary miRNAs |
| Pri-miRNAs  | Primary miRNAs |
| PTEN        | Phosphatase and tensin homolog |
| Rictor      | Rapamycin-insensitive companion of mTOR |
| RISCs       | RNA-induced silencing complex |
| S6K1        | Ribosomal protein S6 kinase beta 1 |
| shRNAs      | Short heterogenous RNAs |
| siRNA       | Small interfering RNA |
| snoRNAs     | Small nucleolar RNAs |
| snRNAs      | Small nuclear RNAs |
| TS          | Thymidylate synthase |
| UTR         | Untranslated Region |

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